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Name of Candidate: Lisseth C. Calvio
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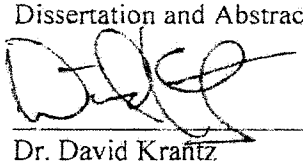

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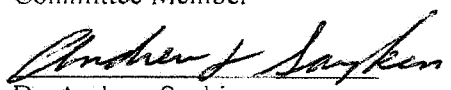

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14. ABSTRACT

A subset of breast cancer survivors (BCS) experience cognitive deficits that may impact work productivity. There are two methods of measuring cognitive limitations: self-report (perceived) and neuropsychological testing (observed). The gold standard for assessment of cognitive function is observed measurement; however, it is unclear how these measures relate to each other and to work productivity. The purpose of this study is to investigate factors that impact work limitations in BCS and a Non-Cancer Comparison Group (NCCG) and to investigate the relationship between perceived and observed measures of cognitive limitations, accounting for possible confounders in both groups as it pertains to work limitations.

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Measures of cognitive limitations and their relation to perceived work limitations in breast cancer survivors

Lisseth C. Calvio, M.S.

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ABSTRACT

Title of Dissertation: Measures of cognitive limitations and their relation to work function in breast cancer survivors

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Objective: A subset of breast cancer survivors (BCS) experience cognitive deficits that may impact work productivity. There are two methods of measuring cognitive limitations: self-report (perceived) and neuropsychological testing (observed). The gold standard for assessment of cognitive function is observed measurement; however, it is unclear how these measures relate to each other and to work productivity. The purpose of this study is to investigate factors that impact work limitations in BCS and a Non-Cancer Comparison Group (NCCG), and to investigate the relationship between perceived and observed measures of cognitive limitations, accounting for possible confounders in both groups as it pertains to work limitations.

Methods: Seventy-five working BCS working a minimum of 1-year post-primary treatment and 75 women in a NCCG completed an online survey consisting of several measures (e.g., demographic factors, work limitation, depressive symptoms, anxiety, pain, physical fatigue). Both groups also completed measures of perceived cognitive limitations and an Internet based neuropsychological screen (CNS-Vital Signs). Partial correlations, Multivariate

Analysis of Covariance (MANCOVA) and a series of hierarchical linear regressions and logistic regressions were conducted in order to: 1) determine whether BCS endorsed greater symptom burden (e.g., depressive and anxiety symptoms, fatigue) than NCCG; 2) determine the contributions of perceived and observed cognitive limitations on work limitations after accounting for proposed confounders; 3) replicate previous work indicating a stronger relationship between physical fatigue and work limitations in BCS and a stronger relationship between depressive symptoms and work limitations in NCCG; and 4) evaluate if the relationship between observed and perceived cognitive limitations measures will be significantly different.

Results: BCS reported greater physical fatigue (p=0.000), general fatigue (p=0.000), and depressive symptoms (p=0.000) than the NCCG. BCS reported significantly more perceived cognitive limitations (p=0.000) despite performing similarly to NCCG on observed cognitive tests. Symptom burden measures (R^2 Change=0.43 for BCS, p=0.000; R^2 Change= 0.25 for NCCG, p=0.000) accounted for a significant amount of variance in work limitations. After accounting for proposed confounders, self-reported cognitive limitations (R^2 Change=0.19 for BCS, p=0.000; R^2 Change= 0.28 for NCCG, p=0.000) accounted for more variance in work limitations than performance tests (R^2 Change=0.04 for BCS, p=0.57; R^2 Change= 0.10 for NCCG, p=0.14).

Conclusions: Results suggest that treating fatigue, depressive symptoms, and perceived cognitive limitations may improve perceived functioning at work for both BCS and women without a cancer history. Measures of perceived cognitive

and work function should be incorporated when assessing cognitive performance. Perceived cognitive impairment and symptom burden should be evaluated and psychoeducation on treatment of symptom burden should be provided when assessing work limitations of both BCS and women without a cancer history. Efforts should be made to develop a brief measure that captures both observed and perceived cognitive limitations.

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Who is a Cancer Survivor?

The term “cancer survivor” was coined by Fitzhugh Mullan (1985), a physician who was diagnosed with mediastinal seminoma. Although researchers have differed in their operational definitions of “cancer survivor,” a cancer survivor is commonly defined as an individual diagnosed with cancer, regardless of the course of illness, from time of diagnosis until death (Aziz & Rowland, 2003; Mullan, 1985). Mullan classified cancer survivorship into three phases: acute, extended, and permanent.

Acute survival begins at diagnosis and concludes at the completion of the first treatment effort. During this time, individuals often face their own mortality, and as a result, high levels of fear and anxiety are frequently experienced in this phase. Fatigue, reduced aerobic capacity, and physical limitations experienced during the acute survival stage can influence home and work situations (Aziz & Rowland, 2003; Mullan, 1985).

Extended survival is classified as the time period from the end of treatment until the risk of recurrence has diminished significantly. This period can be characterized by a fear of recurrence of the cancer. This phase is also dominated by the survivor’s effort to return to “normalcy,” or usual activities prior to cancer, and returning-to-work (Aziz & Rowland, 2003; Mullan, 1985).

The concept of permanent survivorship is considered to be when the possibility of recurrence is sufficiently lowered that the cancer is considered to be arrested (Aziz & Rowland, 2003; Mullan, 1985). During permanent survivorship,

the survivor is often faced with late and long-term effects of cancer and cancer treatment. Late effects of cancer are defined as unrecognized toxicities that manifest after a time period following termination of treatment. Long-term effects of cancer refer to side effects or complications related to the cancer experience that begin during treatment and persist thereafter. For example, cognitive difficulties and fatigue may be classified as either late effects or long-term effects of cancer treatment (Aziz & Rowland, 2003). It is important to note that these are conceptualized classifications with no distinct timeline and each survivor's experience is unique and may not neatly fit into these categories or characteristics (Aziz & Rowland, 2003). For example, a cancer survivor may experience several years being "cancer-free" or without an episode of recurrence and have a significantly decreased risk of recurrence; however, he or she may still have a substantial fear of recurrence.

In this study, we looked at breast cancer survivors (BCS) between 1 and 10 years after the completion of primary treatment. Primary treatment in this study was defined as surgery, radiation, chemotherapy or combination of these treatments. By Mullan's definition, this would include individuals who are in the extended and permanent phase of survivorship. Survivors in the acute phase often experience both short-term and long-term effects of cancer with high intensity. Acute cancer survivors were excluded in order to control for the severe emotional and physical impact that may be initially caused by cancer diagnosis and treatment (Mullan, 1985). The variable of interest was cognitive limitations and work limitations. In a subset of survivors that express cognitive limitations,

these limitations tend to be pronounced during the acute phase, and decrease yet often remain present during the extended and permanent phase of survivorship and may impact their functioning in areas such as work (Ahles et al., 2003; Brezden et al., 2000; Feuerstein et al., 2007).

Cancer Epidemiology

Approximately 1.3 million Americans receive a cancer diagnosis each year, and this number is projected to double by 2055 (U.S. Cancer Statistics Working Group, 2004). The cancer survivor community is increasing as the incidence of cancer diagnoses is increasing. Individuals surviving cancer five or more years following treatment increased from 25 percent in 1960 (Mullan, 1985) to 49.6 percent in 1976 and 64.1 percent in 2000 (Centers for Disease Control and Prevention, 2004). Consequently, the cancer survivor population increased from three million in 1971 to almost 10 million in 2001 and over 11 million in 2007 (CDC, 2008; Jemal et al., 2006; Ries et al., 2006; Rowland, Hewitt, & Ganz, 2006; U.S. Cancer Statistics Working Group, 2004). As a result, a disease that was once considered a death sentence is now often a chronic illness. Early detection through increased screening, treatment advances, prevention of cancer recurrence and secondary disease occurrence, and decreases in mortality from other causes are the reason for an increase in survivorship (Carlson, 2007; Rowland, Hewitt, & Ganz, 2006).

Incidence and mortality rates of cancer differ by gender and race (U.S. Cancer Statistics Working Group, 2004). For men, the highest incidence rate is for prostate cancer, followed by lung and colon cancer. This trend is consistent

across the different races and ethnicities (Caucasian, African-American, Hispanic, and Asian-American/Pacific Islander). For women, the highest incidence rate is for breast cancer, followed by lung and colon cancer. This trend in incident rates is consistent across different ethnicities and races (Caucasian, African-American, Hispanic, and Asian-American/Pacific Islander; U.S. Cancer Statistics Working Group, 2004).

Although the trends in types of cancers are similar across the ethnic groups, there is disparity in the actual number of incidence and mortality rates. For example, African Americans (both male and female) have a 34 percent higher cancer mortality rate than Caucasians, and 200 percent higher cancer mortality rate than Asians/Pacific Islanders. Higher mortality rates of colon and breast cancer are found in African American women than women of any other ethnic/racial group. African American men have the highest mortality rates for colon, lung and prostate cancer. Hispanics have higher rates of cervical, gallbladder, esophageal, and stomach cancers (U.S. Department of Health and Human Services, 2000). These differences between gender and ethnicities should be considered when studying cancer survivors (U.S. Department of Health and Human Services, 2000). Mortality rates for women differ by ethnicity. Hispanic women have a higher mortality rate of breast cancer, followed by lung and colon cancer. Caucasian, Asian-American, and African-American women have higher mortality rates of lung cancer, followed by breast and colon cancer (U.S. Cancer Statistics Working Group, 2004).

Breast Cancer Epidemiology

Breast cancer is the most common form of cancer for women in the United States. Breast cancer is the second most lethal cancer for women (lung cancer being first) and the main cause of death for women ages 45 to 55 (Jemal et al., 2006; Ries et al., 2006). The yearly incidence estimate of breast cancer diagnosis in the United States is approximately 182,460 women. The yearly mortality estimates for breast cancer in the United States is 40,480 women (Ries et al., 2006). One in six (16.7%) women will develop breast cancer in their lifetime and one in nine (11.1%) will develop invasive breast cancer. BCS are the largest female cancer survivor group in the United States, as 41 percent of female cancer survivors are BCS. As of January 1, 2005, there were 2,477,847 women BCS in the United States (Ries et al., 2006). These figures demonstrate that the BCS are one of the largest growing groups of survivors and will continue to grow in the United States. Furthermore, research investigating return-to-work patterns (Bouknight, Bradley, & Luo, 2006) and cognitive function post-cancer (Tannock, Ahles, Ganz, & Van Dam, 2004; Vardy et al., 2007) is being conducted with this cohort. Due to the large available populace and growing scientific literature with this cohort, female BCS were the focus of this study.

Incidence and mortality rates differ within the United States by ethnicity. According to the American Cancer Institute (ACS, 2005), Caucasian women (141.1 per 100,000) have the highest incidence rates of breast cancer, followed by African American women (119.4 per 100,000), Asian Americans/Pacific Islander women (96.6 per 100,000), Hispanic women (89.9 per 100,000), and

American Indians/Alaska Native women (54.8 per 100,000). However, mortality rates do not follow the same ethnic trend as incidence. For example, African American women have a higher mortality rate than Caucasian women. Furthermore, African American women are more likely to be diagnosed at a more advanced stage and diagnosed with more aggressive forms of breast cancer. This health disparity is partly explained by differences in lifestyle, socioeconomic status, cultural differences in medical seeking behavior, and access to adequate medical screening and treatment (Bradley, Given, & Roberts, 2002; Smigal et al., 2006).

Age is another important factor when considering demographics of BCS. Approximately 58.3 percent of new breast cancer cases per year are under the age of 65. Ages 50 through 59 have the highest incidence of breast caner, followed by 60-69, and 40-49. As a result, the majority of female breast cancer patients are within US working age, between 18 and 65 years old (ACS, 2003, 2005).

Women are 100 times more likely to be diagnosed with breast cancer than men. Annually in the United States, approximately 213,000 women are diagnosed with invasive breast cancer compared to 1,700 men (Jemal et al., 2006). Due to the low incidence rate of male breast cancer cases, in this review, we focused our study on female BCS. Prognosis for BCS is relatively good as 92 percent of breast cancers are diagnosed at stages 0 through III (non-metastasized). The five-year survival rate for invasive BCS is 98 percent for localized breast cancer and 83.5 percent for regional (spread to regional lymph

nodes or directly around the primary site) breast cancer. Metastasized breast cancer (stage IV) has a 26.7 percent five-year survival rate (ACS, 2005; Ries et al., 2006). This indicates that the growing breast cancer survivor community includes a high proportion of women under the age of 65, who will survive for many years after diagnosis.

Breast Cancer

Anatomy. The anatomy of the breast must be explained in order to understand diagnosis and treatment of breast cancer. The breast is composed of skin, subcutaneous tissue, adipose tissue, breast tissue, ducts, lobules, alveolus, and an excretory sinus. The breast contains 15 to 20 lobes of glandular tissue supported by a network of fibrous connective tissue. Each lobe is subdivided into lobules, which consist of branched tubuloalveolar glands that end in a lactiferous duct. The ducts dilate into lactiferous sinuses, which are located beneath the nipple, and these sinuses open into the nipple. For diagnosis and treatment purposes, the breast is often divided into quadrants. Posteriorally, the upper quadrants of the breasts are on the fascia of the pectoralis major muscle. The breast is surrounded by the fascia of the serratus anterior and supported by Cooper's ligaments (bands of fibrous tissue). Size of the breast depends on amount of adipose tissue (Greenfield, 2001). Understanding the basics of the breast anatomy assists in the understanding of the pathology of breast cancer, as well as the differences in treatment options.

Classification of Breast Cancer. There are two main classification systems for breast cancer: the staging and TNM classification system. Size of primary

tumor, presence of chest wall invasion, and presence of metastasis (local or distal) are considered when classifying a breast tumor (Greene, 2002).

The staging system ranges from stages 0 to IV. Stage 0 represents a non-invasive or in situ cancer. Stage I and II are early stages of invasive breast cancer. Stage II is divided into two substages (Stage IIA and IIB), and Stage III is divided into three substages (Stage IIIA, IIB, and IIIC). Stage III is considered invasive locally advanced breast cancer. Stage IV represents metastasized breast cancer (Greene, 2002).

The TNM classification system incorporates several features of the tumor: primary tumor (T), regional lymph nodes (N), and distant metastasis (M). Each of the classifications has different levels that define the magnitude of that property. For instance, the T (primary tumor) classification has several levels ranging from TX, which refers to the primary tumor cannot be assessed to T4, which represents tumor of any size that has extended into the chest wall or skin. The staging and TNM classification systems are complimentary and assist physicians in determining appropriate treatment (Greene, 2002).

Histology. The two major histological categories for breast cancer are in situ and invasive carcinoma. In situ cancers are usually restricted to the ductal-lobular system and are less likely to metastasize (Greenfield, 2001). In situ are categorized as not otherwise specified (NOS), intraductal, or Paget's Disease of the nipple and intraductal. Invasive breast cancer is more aggressive than in situ. Invasive breast cancer is defined as "tumor cells, which have crossed the basement membrane and have the biologic capacity to metastasize" (Greenfield,

2001, p. 1357). Invasive tumors are categorized as NOS, ductal, inflammatory, medullary with lymphoid stroma, medullary (NOS), mucinous, papillary, lobular, tubular, Paget's Disease and infiltrating, undifferentiated, squamous cell, adenoid cystic, secretory, or cribriform (Greene, 2002).

Carcinoma In Situ. Lobular carcinomas in situ (LCIS) are small, solid, and usually are without calcifications (Greenfield, 2001). Prognosis for LCIS is usually good. A small percentage (21 percent over 15 years) of LCIS becomes invasive cancer; however, an aggressive variant of LCIS exists that increases the risk of developing invasive cancer. After LCIS is diagnosed in one breast, the other breast has equal risk of developing an invasive tumor. In some cases, LCIS is treated by clinical observation only. However, for certain situations, such as strong family history of breast cancer, certain genetic mutations, or when the patient has extreme levels of anxiety, LCIS is treated with bilateral prophylactic mastectomy or by using selective estrogen receptor modulators tamoxifen or raloxifene (National Comprehensive Cancer Network, 2007).

Approximately 30 to 50 percent of the breast malignancies identified by biopsies are ductal carcinoma in situ (DCIS; Greenfield, 2001). DCIS that do spread to two or more quadrants of the breast are treated with total mastectomy without lymph node dissection or breast conserving therapy (excision followed by radiation therapy). DCIS that are confined can be treated with breast conserving therapy or breast conserving surgery (excision only) followed by clinical observation. Axillary node dissection and tamoxifen are not indicated for this form of in situ cancer if there is no invasive component to the tumor. However, for

tumors with invasive potential, such as atypical ductal hyperplasia, tamoxifen can reduce risk of invasive cancer by 86 percent. Adding tamoxifen to breast conserving therapy for Estrogen Receptor (ER)-positive DCIS has reduced the relative risk of recurrence by 37 percent (National Comprehensive Cancer Network, 2007)

Invasive Breast Carcinoma. Once a breast tumor has been identified, invasive breast cancer is usually tested and classified by considering patient's medical and family history, as well as a series of medical exams (e.g., a physical exam, blood cell count, liver function tests, platelet count, chest imaging, mammography). Tests investigating the human epidermal growth factor receptor (HER2) tumor status are usually necessary to help determine appropriate treatment (National Comprehensive Cancer Network, 2007).

Approximately 60 to 80 percent of breast cancer cases are infiltrating ductal carcinoma, which is a type of invasive cancer that is characterized by firm, irregular, grayish white lesions, which microscopically are mixed tumors. Approximately 10 percent of all breast cancers are infiltrating lobular carcinomas, or malignant cells which usually grow circumferentially around ducts and lobules. Infiltrating lobular tumors are harder to find because they may not produce characteristic lesions, as with infiltrating ductal carcinoma. Infiltrating lobular carcinoma is more likely to metastasize beyond the breast (Greenfield, 2001).

Treatment

Overview. Several surgical and adjuvant treatment options are available for breast cancer. Treatment appropriateness is dependent on several factors,

including histology and tumor stage, lymph node status, hormone-receptor status, HER2 status, age at diagnosis, and menopausal status (Clarke et al., 2005; National Comprehensive Cancer Network, 2007).

Less aggressive non-invasive (in situ) tumors are less likely to spread or affect axillary nodes and can be treated by clinical observation or nodal dissection (National Comprehensive Cancer Network, 2007). There are occasions where more aggressive treatment such as a lumpectomy, breast conserving therapy, or mastectomy may be appropriate; however, in general, adjuvant chemotherapy is not recommended for this histological type of cancer (National Comprehensive Cancer Network, 2007).

A distinction in invasive tumors is node status, which refers to the spread of cancer to the lymph nodes (Clarke et al., 2005). For node positive breast cancers, axillary nodal dissection, or removal of nodes, with an initial systemic chemotherapy therapy may be appropriate, followed by a local therapy for the breast. The purpose of axillary dissection is to terminate metastatic cancer in the axillary nodes (National Health and Medical Research Council, 2001). Breast conservation therapy is generally recommended for early stage I and II breast cancer. Other forms of surgical treatment involve modified radical mastectomy and mastectomy with or without reconstruction. Adjuvant therapy may be required after surgery. Advances in adjuvant therapy have been shown to significantly reduced disease recurrence and death (Clarke et al., 2005; National Comprehensive Cancer Network, 2007).

Mastectomy. All women with invasive breast tumors are treated with surgical resectioning, either by mastectomy or lumpectomy. Mastectomy grossly refers to the partial or complete removal of one or both breasts. Modified radical mastectomy refers to an operation where the axillary nodes, breast tissue, and fascia of the pectoralis major muscle are removed. Mastectomy and immediate reconstruction involves expanding the breast tissue, removal of the expander, and inserting tissue expanders or a permanent breast implant immediately after the modified radical mastectomy.

It is beneficial to conduct reconstruction surgery immediately after a mastectomy because the recovery time is approximately equal to women who only receive a mastectomy. However, women who opt for the immediate reconstruction often require a second surgical procedure to treat complications (e.g., breast implant deflation, capsular contracture) and the reconstruction has cosmetic limitations, particularly in women with large breasts. Radiation exposure following the mastectomy and reconstructive surgery increases the incidence of implant loss and poor cosmetic outcome. An alternative to reconstruction via implants involves using tissue flaps called transverse rectus abdominis myocutaneous (TRAM) flap. Using these skin flaps allows for a more natural look and feel than implants, and TRAM flaps have fewer side effects to radiation exposure (Greenfield, 2001).

Breast Conserving Therapy. Breast conserving therapy involves removing the tumor (lumpectomy) without removing excessive amounts of normal breast tissue, followed by radiation therapy of the tumor site (partial irradiation) or entire

breast (Clarke et al., 2005). Breast conserving therapy is considered successful when it is shown to reduce the tumor on a microscopic level and is controlled by radiation, radiation therapy is safely administered, and local recurrences are quickly detected (Greenfield, 2001). For early staged breast cancer, breast-conserving therapy has resulted in equivalent survival rates as mastectomy. Breast cancer patients are usually offered adjuvant chemotherapy post-surgery. Breast cancer patients whose tumors express the estrogen receptor are offered hormonal therapy post surgery (Fan et al., 2005a).

For many years, the combination of mastectomy and radiation therapy was the standard of treatment for DCIS (Greenfield, 2001). However, this was considered a radical treatment for a cancer that had a 10-to15 percent recurrence rate over 10 years and a low death rate (e.g., 14 deaths in 814 patients in eight years). Randomized control trials have found that breast conserving therapy with radiation therapy effectively treats DCIS along with significantly reducing the rate of recurrence over eight years. As a result, there has been an increasing shift to treating DCIS breast cancer with breast conserving therapy (Greenfield, 2001). The standard of care for DCIS and early-stage (I and II) breast cancer is now considered breast-conservation surgery in conjunction with radiotherapy (Meric et al., 2002).

Despite the benefits of breast conservation therapy, there are several factors that determine its appropriateness for a patient. Risk of in-breast recurrence is the biggest reason for not recommending breast-conserving therapy. Breast conservation therapy is usually not recommended if the

estimated risk of recurrence is greater than 10 percent over the next five to 10 years, even after the combination of surgery and radiation. Breast conservation therapy is contraindicated for women who have positive resection margins after re-excision attempts, two or more primary tumors in distinct quadrants of the same breast, diffuse malignant-appearing microcalcifications, history of radiation therapy to the breast region that would result in an accumulation of a high radiation dose, and are pregnant (with some exceptions). Pregnant women can receive breast-conserving surgery if the surgery itself is performed during the third trimester and the radiation is given post-partum. Other relative contraindications include patients with a history of connective tissue disease due to the possible side effect of radiation leading to dermal complications; women with a large tumor in a small breast due to unfavorable cosmetic factors; and women with large or pendulous breasts if homogeneity in radiation dose cannot be obtained (Greenfield, 2001).

Radiation Therapy. Radiation is given to eliminate any residual disease that may be resistant to chemotherapy and minimize the chance of locoregional recurrence of the disease. Breast conserving surgery alone results in a five-year recurrence risk of 26.7 percent. When breast-conserving surgery is combined with radiotherapy, the observed five-year recurrence risk is 7.7 percent. Fifteen year mortality risk for breast conserving surgery alone is 33.2 percent compared to 28.0 percent for BCS treated with breast conserving surgery and radiotherapy (Clarke et al., 2005). A meta-analysis of 78 randomized control trials has looked at studies investigating the effects of radiation therapy with breast conserving

surgery or mastectomy (Clarke et al., 2005). The meta-analysis found that radiation therapy decreases five-year reduction in risk for both node negative and node positive survivors. For example, radiation therapy in combination with breast conserving surgery had a 30.1 percent absolute risk of recurrence in node positive breast cancer patients, compared to a 16.1 percent absolute risk of recurrence in node negative patients. These studies indicate that the largest benefit of adding radiation therapy to surgery is in the reduction of local recurrence and there is a more pronounced effect on node-positive breast cancer for five year absolute reduction (Clarke et al., 2005).

Ragaz and colleagues (1997) found that radiation therapy in combination with chemotherapy after a mastectomy reduces rates of recurrence by 33 percent and overall mortality by 29 percent in node-positive premenopausal BCS 15 years after diagnosis. Whelan and colleagues (2002) investigated the effects of different irradiation schedules and observed that a shorter course of radiation therapy (42.5 Gy in 16 fractions over 22 days) with breast conserving therapy had similar results to the longer regimen of 50 Gy in 25 fractions over 35 days with breast conserving surgery.

Radiation therapy has been shown to be effective at reducing locoregional recurrence, lowering risk of death, and increasing disease-free survival in pre- and post-menopausal women with severe forms of the disease, such as tumors greater than five centimeters or greater than four positive axillary nodes (Clarke et al., 2005). Radiation therapy appears to be more effective at reducing

recurrence and improving overall survival in node positive breast cancer when combined with chemotherapy (Ragaz et al., 1997).

Chemotherapy. Research indicates that there are many benefits to adding chemotherapy to the adjuvant regimen when adjuvant therapy is appropriate to both pre- and post-menopausal breast cancer patients. However, there is a higher benefit for pre-menopausal women, possibly due to chemotherapy's hormonal affect. Chemotherapy is considered part of the adjuvant standard of care for ER-negative tumors. On the other hand, chemotherapy with ER-positive tumors is more controversial, especially with node-negative cancer (Clarke et al., 2005).

Higher cumulative doses of anthracycline chemotherapy have been associated with congestive cardiac failure. Due to possible cardiac effects, it is not recommended that chemotherapy and radiation therapy be given simultaneously (National Health and Medical Research Council, 2001). Radiation therapy can be delayed up to six months after either breast conservation surgery or mastectomy in order to allow for the chemotherapy regimen. As an adjuvant therapy, chemotherapy is given after local therapy; however, chemotherapy can also be given prior to surgery, as is the case in neoadjuvant therapy. Women with advanced or inflammatory breast cancer are treated with neoadjuvant therapy (National Comprehensive Cancer Network, 2007; National Health and Medical Research Council, 2001).

Other Adjuvant Therapy. In addition to chemotherapy, adjuvant therapy could involve hormone therapy (e.g., tamoxifen), aromatase inhibitors,

humanized monoclonal antibody or a combination of these treatments (National Comprehensive Cancer Network, 2007). Treatment appropriateness depends on several factors, such as gene expression, hormonal receptor expression, lymph node status, menopausal status, and age at diagnosis.

An important factor in determining appropriate treatment involves status of the human epidermal growth factor receptor (HER2). HER2 and its associated gene are involved in cell growth. Over-expression of HER2 is associated with a more aggressive breast cancer, as it is more likely to metastasize and have a worse prognosis. HER2 breast cancer occurs in 20 percent of breast cancer cases. Trastuzumab (Herceptin ®), a monoclonal antibody, either by itself or in combination with chemotherapy, has been shown to be effective in treating over-expression of HER2 (National Comprehensive Cancer Network, 2007).

Tamoxifen is considered to be tolerable. However, there are several side effects associated with long-term use of tamoxifen. Although tamoxifen acts as an estrogen antagonist in the breast, it has estrogen partial agonist effects on the endometrium. This results in some benefits, such as increased defense against bone loss for post-menopausal women. Common negative side effects of tamoxifen include thromboembolic (blood clotting) disorders, endometrial cancer, and other gynecological complications (Baum et al., 2002). Animal studies have shown that tamoxifen can cross the blood brain barrier and deregulate serotonin and dopamine levels, as well as affect cytokine levels and initiate an immunologic response (Lien et al., 1991; Wefel, Witgert, & Meyers, 2008). Chen and colleagues (2002) demonstrated that the administration of tamoxifen was

associated with decline in spatial memory in rats (Chen et al., 2002). A neurophysiological study demonstrated that BCS who were treated with the combination of chemotherapy and tamoxifen were more likely to show patterns of hypometabolism in the lentiform nucleus than BCS who were treated with chemotherapy alone (Silverman et al., 2006). Hence, tamoxifen can potentially impact brain structures and activity that can lead to changes in cognitive and emotional functioning (Wefel, Witgert, & Meyers, 2008).

Aromatase inhibitors have been compared to tamoxifen. In post-menopausal women, aromatase inhibitors work by inhibiting the enzyme that converts androgens to estrogen, also called aromatization. Aromatase inhibitors are tolerable, but are associated with increased musculoskeletal disorders and fractures (Baum et al., 2002). Aromatase inhibitors have been found to be as effective as tamoxifen in certain breast cancers (ER positive post-menopausal women), while having a more tolerable gynecological side effect profile than tamoxifen (Baum et al., 2002). Aromatase inhibitors have also been associated with improved disease-free survival, time to recurrence, and decreased incidence of contralateral breast cancer when compared to tamoxifen only treatment (Baum et al., 2002).

Menopausal status is important when selecting aromatase inhibitors or tamoxifen treatment. Aromatase inhibitors are contraindicated for pre-menopausal women, as aromatase inhibitors cause a reduction in estrogen production, which results in a reduced feedback of estrogen to the hypothalamus, which leads the body to produce more estrogen. Aromatase inhibitors have an

opposite effect (increase estrogen production) in pre-menopausal women. As a result, tamoxifen and ovarian ablation are the adjuvant therapies recommended to pre-menopausal women (Mokbel, 2002; National Comprehensive Cancer Network, 2007). Chemotherapy also acts to suppress estrogen production in pre-menopausal women, which may result in early menopause. While these treatments increase cancer-free survival and recurrence, they may leave behind other side effects that impact quality of life in survivors (Del Mastro, Venturini, Sertoli, & Rosso, 1997).

Age at diagnosis also impacts treatment planning. Evidence suggests that female breast cancer patients under the age of 50 benefit more from anthracycline-based polychemotherapy (such as fluorouracil, doxorubicin, and cyclophosphamide) than patients between the ages of 50 and 69. A review of randomized control trials found that six months of anthracycline-based polychemotherapy led to a 38 percent reduction in the annual mortality rate for women under the age of 50 at diagnosis. This regimen had a 20 percent reduction in the annual mortality rate for women between the ages of 50 and 69. The benefits of chemotherapy are unclear for women over the age of 70, as few women in this age group have enrolled in randomized control trials (National Comprehensive Cancer Network, 2007). This data suggests that chemotherapy disproportionately benefits younger women, which could be related to the ovarian suppression effect of chemotherapy (Berry et al., 2006).

Lymph node status has also been investigated with regards to treatment effects. Tamoxifen alone or tamoxifen and three cycles of chemotherapy

(cyclophosphamide, methotrexate, and fluorouracil) were administered to lymph node negative, ER positive and ER negative, post-menopausal BCS. Disease free survival (DFS) and overall survival (OS) were calculated at a median of 71 months after treatment. The results indicated that the lymph node negative BCS with ER negative post-menopausal breast cancer benefit more from combination systematic adjuvant chemotherapy and tamoxifen than lymph node negative ER positive post-menopausal BCS (International Breast Cancer Study Group, 2002).

Berry and colleagues (2006) investigated the effect of three different adjuvant chemotherapy regimens on node-positive post-menopausal BCS. The results were complimentary to the International Breast Cancer Study Group (2002) study, as node positive, ER negative, post-menopausal survivors benefited more from chemotherapy than lymph positive, ER positive post-menopausal survivors. For instance, after three trials of chemotherapy, ER negative node positive cancer patients had a 55 percent reduction in relative risk of recurrence, compared to 26 percent reduction in ER positive node positive patients (Berry et al., 2006).

Several factors (e.g., age at diagnosis, menopausal status, HER2 status, and hormonal receptor status of the tumor) dictate adjuvant treatment appropriateness. Deferring adjuvant treatments have varying side effect profiles, which may impact functioning. As a result, adjuvant treatments must be considered when assessing possible long-term complications, such as cognitive limitations.

Common Side Effects of Cancer Treatment. Side effects of cancer treatment vary due to modality of treatment, intensity or dosage of treatment, number of chemical agents used, organ exposure, and duration of exposure to chemicals or procedures (National Health and Medical Research Council, 2001). For example, chemotherapy has short-term side effects such as nausea, vomiting, and alopecia; and long-term side effects such as infertility/amenorrhea, fatigue and cognitive impairment. Tamoxifen is associated with hot flushes, higher risk for endometrial cancer, growth of benign fibroids, deep vein thrombosis, and pulmonary embolism or stroke. The focus of this study was on the long-term side effect of cognitive impairment.

Symptom Burden

Cancer treatment has been associated with long-term physiological, cognitive, and psychiatric changes. The next sections will discuss these changes.

Quality of life. Health-related quality of life (HRQOL) and overall quality of life (QOL) may also be impacted by the cancer experience one-to-two years post-diagnosis (Ahn et al., 2007; Fan et al., 2005b). Fan and colleagues (2005b) compared health related QOL of disease-free BCS up to two-years post diagnosis with females from the general population. Approximately one-third of the breast cancer survivor sample had received breast-conserving surgery and two-thirds received mastectomy treatment. Of the survivors that received breast conservation treatment, 57 percent received chemotherapy, 82 percent received radiation therapy, and 48 percent underwent hormone therapy. Of the survivors that received mastectomies, 65 percent received chemotherapy, 18 percent

received radiation therapy, and 48 percent received hormonal therapy. Compared to the general female population, BCS reported significantly less physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The study found that individuals who received mastectomy had lower social functioning and poorer body image than those who received breast conservation surgery. Older BCS reported having better social and emotional functioning and future perspective; however, older survivors also reported poorer physical as well as sexual functioning and enjoyment than younger BCS. Depressive symptoms and cancer-related fatigue were the strongest predictors of decreased health related QOL.

Fan and colleagues (2005b) found that overall QOL was worse for BCS than a matched-control group at baseline assessment. These differences in QOL between BCS and matched-controls decreased with time. Overall, the symptoms experienced by BCS were most pronounced immediately after cancer treatment and decreased over time, although most survivors remained symptomatic (e.g., cognitive limitations, fatigue) at two years post-treatment (Fan et al., 2005b).

Kenne-Sarenmalm and colleagues (2008) investigated factors contributing to distress and quality of life in 56 BCS and found that fatigue, pain, and depressive symptoms explained approximately 72 percent of the variance in distress measures. This study also found that distress accounted for almost half of the variance in quality of life of these BCS. The Kenne-Sarenmalm et al. (2008) study concluded that fatigue, pain and depression were important and persistent contributors to distress levels and quality of life of BCS.

Cancer-related fatigue. Cancer-related fatigue has been defined as, “distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with functioning” (NCCN, 2009, p. FT-1). Fatigue may impact several domains of functioning, such as physical, mental, and emotional functioning and can be present for several years following cancer diagnosis and treatment (NCCN, 2009; Stein, Jacobsen, Blanchard, & Thors, 2004; Valentine & Meyers, 2001).

Cancer-related fatigue has been found in up to 96 percent of breast cancer patients during treatment (Wagner & Cella, 2004). This type of fatigue has been associated with treatment factors (i.e., modality and length of treatment) and has been found to persist for years after cancer treatment (Fan, et al., 2005a; Ganz & Bower, 2007; Tchen, et al., 2003; Wagner & Cella, 2004). Servaes, Verhagen and Bleijenberg (2002) found that cancer-related fatigue was present in approximately 40 percent of BCS who were on average 29 months post-treatment.

Mehnert and colleagues (2007) found that cancer-related fatigue was present in 82 percent of their sample of BCS (BCS), five years post-standard adjuvant and high-dose chemotherapy. Arndt and colleagues (2006) reported that after accounting for age, fatigue accounted between 30 percent and 50 percent of the variance in a variety of measures of function (e.g., physical, emotional, role, cognitive, and social function), body image, future perspective, and overall quality of life in a sample of 314 BCS, one year post-diagnosis. Long

term complications associated with chemotherapy include cancer-related fatigue (Fan et al., 2005b; Tchen et al., 2003). Fan and colleagues (2005b) conducted a longitudinal study of breast cancer patients compared to matched controls. This study found that symptom burden of cancer-related fatigue significantly decreased with time in BCS, two years post-treatment. However, BCS still experienced higher levels of cancer-related fatigue than their age-matched controls. Servaes and colleagues (2007) conducted a longitudinal study where they tracked monthly fatigue levels of 150 BCS (29 months post-treatment at baseline) for two years. The results of this study showed that 56 percent of BCS experienced heightened/severe fatigue at baseline. Although endorsement of heightened/severe fatigue decreased to 45 percent at the two years of follow-up, the same participants tended to endorse the fatigue symptoms indicating that these symptoms persisted throughout the trajectory. BCS who endorsed high anxiety, impairment in role functioning and low control over fatigue symptoms at baseline were likely to report persistent fatigue over the two years they were monitored. These studies highlight the importance of accounting for cancer-related fatigue when assessing functionality of BCS.

Pain. Pain has been reported in as many as 33 percent to 70 percent of BCS several years post-diagnosis (Avis, Crawford, & Manuel, 2005; Deimling et al., 2006; Ganz et al., 2003). Pain experienced by BCS can vary from comorbid arthritis and osteoporosis (Schultz, Beck, Stava, Vassilopoulou-Sellin, 2003) to pain associated with the sequelae of cancer diagnosis and treatment (Baron et al., 2007; Peuckmann et al., 2008). Chronic pain (≥ six months) was compared

between long-term BCS (≥ five years post-treatment) and women who had never had cancer in a population based study (Peuckmann et al, 2008). After accounting for age, the prevalence of chronic pain was significantly higher in the BCS population (42 percent) than women in the general population (32 percent). Pain commonly reported by BCS included paraesthesia (tingling, prickling or numbness on skin; 47 percent), chronic pain (pain most days lasting greater than or equal to six months; 29 percent), arm/shoulder swelling (25 percent), phantom sensations (19 percent), and allodynia (i.e., pain in response to a non-painful stimulus; 15 percent). Pain experienced after breast cancer has been associated with reduced functioning, including at work (Avis, Crawford, & Manuel, 2002; Deimling et al., 2005; Maunsell et al., 2004; Peuckmann et al, 2008). This indicates that different forms of pain are commonly experienced by BCS years after diagnosis and may limit work productivity in this population. As a result, pain levels were assessed in this study.

Amenorrhea. Approximately a quarter of women diagnosed with breast cancer are premenopausal. For these women, up to 89 percent experience amenorrhea or premature menopause, that is often called chemotherapy-induced or treatment-induced menopause (Del Mastro et al., 1997). Premature menopause can be devastating to many women as they will no longer be able to bear children and they experience menopausal symptoms (e.g., hot flushes, genitourinary problems, night sweats, difficulty sleeping) and health risks associated with menopause such as heart disease, osteoporosis, and psychological distress (Goodwin, Ennis, Pritchard, Trudeau, & Hood, 1999).

Goodwin and colleagues (1999) investigated factors that impact premature menopause in BCS treated with lumpectomy and post-operative radiation therapy. In the sample, 45.4 percent was treated with CMF and 13.7 percent was treated with CEF chemotherapy. Twenty-five percent of the sample received adjuvant tamoxifen, of which 53.2 percent received combination of chemotherapy with tamoxifen as their adjuvant regiment. The results indicated that age, chemotherapy, and tamoxifen were predictors of menopause one-year post-treatment. In the Goodwin and colleagues study, there was no difference between CMF and CEF chemotherapy agents. However, Stearns and colleagues (2006) found differences according to age and chemotherapy regiment. For example, 30 to 80 percent of BCS under the age of 40, who received CMF treatment, experienced chemotherapy induced amenorrhea, compared to 60 to 96 percent of survivors over the age of 40 receiving the same regimen. Survivors under the age of 40, who received FEC/FAC treatment, had a 10 to 25 percent incidence of chemotherapy-induced menopause, compared to 80 to 90 percent of survivors over the age of 40 with the same regimen. Accordingly, older women who were treated with both chemotherapy (particularly, CMF or FEC/FAC) and tamoxifen have greater risk of experiencing premature menopause (Goodwin, et al., 1999; Stearns, Schneider, Henry, Hayes, & Flockhart, 2006). Survivors who experienced treatment-induced menopause were 2.6 times more likely to have cognitive decline on multiple measures (Jenkins et al., 2006). As a result, it is important to measure and control for the effects of treatment-induced menopause on cognitive performance.

Animal and neuroendicronology studies have introduced the concept of estrogen having neuroprotective qualities on cognition (McEwen, 1999; Spencer, et al., 2008). Singh and colleagues (1994) indicated that removal of ovaries in rats has been associated with cognitive impairment in learning and memory, which were ameliorated with the use of estrogen treatment (Luine & McEwen, 1983; Singh, Meyer, Millard, & Simpkins, 1994). Small, prospective studies investigating the impact of surgically induced menopause on cognition have found cognitive deficits in visual, auditory, and verbal memory post-surgery (Farrag, Khedr, Abdel-Aleem, & Rageh, 2002; Rice & Morse, 2003; Vearncombe & Pachana, 2008). However, a review conducted by Vearncombe & Pachana (2008) indicated that large randomized controlled trails have found no general effect of surgically induced menopause and inconclusive data on the effects of chemically induced menopause on cognition.

Some of the inconsistency in the research linking induced menopause and cognitive performance can be related to problems with measurement of cognitive function and estrogen levels. Rice & Morse (2003) conducted a review of 20 peer reviewed studies investigating cognitive performance on neuropsychological tests with menopausal women. The review concluded that the research linking cognitive function with estrogen levels was inconsistent, and no specific neuropsychological test or battery was identified as the best or most sensitive measure for investigating cognitive performance in menopausal women. Further complicating the measurement of estrogen levels on cognitive function in the context of BCS is that either chemically or surgically induced menopause can

have several neurobiological effects that may differ from that of naturally occurring menopause. At this point in the research, it is unclear if (naturally occurring or chemically or surgically induced) menopause has an impact on cognitive functioning. Furthermore, it is unclear which tests are most sensitive to detect cognitive differences with these populations (Vearncombe & Pachana, 2008).

Controversy exists as to whether estrogen and menopausal status impacts cognitive limitations found in some BCS. For example, Jenkins and colleagues (2006) found that BCS who experienced treatment-induced menopause were 2.6 times more likely to have cognitive decline on multiple measures. However, a current study by Hermelink and colleagues (2008) evaluating 101 BCS indicated that induced menopause from breast cancer treatment did not significantly contribute to cognitive decline one-year post diagnosis. In addition, this study found that anti-estrogen therapy (i.e., tamoxifen and aromatase Inhibitors) did not impact cognitive performance on performance tests. These discrepant finding in the literature highlight the importance of including menopausal status when measuring cognitive functioning in BCS to evaluate if menopause status is a contributing factor.

Emotional distress. Emotional distress in the form of depressive symptoms have been reported in a wide range of breast cancer patients and survivors in research studies; however, depression is often misdiagnosed or under-diagnosed in oncology and clinical settings (Burgess et al., 2005; Derogatis et al., 1983; Reich, Lesur, & Perdrizet-Chevallier, 2007). Derogatis and colleagues

(1983) investigated the prevalence of psychiatric disorders in three cancer centers with different types of cancer patients. The study reported that 44 percent of cancer patients were diagnosed with a DSM-III psychiatric disorder other than a personality disorder. Eighty-five percent of these patients had anxiety or depression as a central symptom. Sixty-eight percent of those with a psychiatric disorder were diagnosed with an adjustment disorder with depressed or anxious mood, and 13 percent were diagnosed with major affective disorders (e.g., Major Depressive Disorder). Harter and colleagues (2001) found that cancer survivors had a 56.5 percent lifetime risk of developing a term mental disorder. Cancer survivors, one-year post diagnosis, had 23.5 to 33 percent higher prevalence of affective disorders and anxiety disorders than the general population. Furthermore, women had a two-fold risk of developing a mental disorder during their lifetime (Harter et al., 2001). These data indicate the high prevalence of depressive ad anxious symptoms in cancer patients and survivors.

Studies focusing on BCS show similar trends in psychiatric difficulties as studies including numerous types of cancer survivors. A review of nine studies indicated that mood disorders were experienced in up to 60 percent of BCS. Major Depressive Disorder is considered a chronic and often very debilitating disorder. The review found that up to 40 percent of BCS met criteria for Major Depressive Disorder (Reich et al., 2007). Burgess and colleagues (2005) administered a structural clinical interview to 177 early staged BCS. The interviews were given annually for five years. The study used criteria from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised

(DSM-IIIR) to categorize participants as a full case, borderline case, or non-case for anxiety, depression, or combination. The results indicated that up to 48 percent of cancer survivors met criteria for anxiety, depression, or both within the first year post-diagnosis. This prevalence decreased to 25 percent in the second year, 23 percent during the third year, 22 percent during the fourth year, and 15 percent in the fifth year. Forty percent of the women interviewed experienced depressive, anxious, or combination of both symptoms for at least 90 days. These studies indicate that in the first year after diagnosis, women with breast cancer experience depression, anxiety, or both twice as much as the general female population. For many of these women, the duration and intensity of these symptoms are profound. This trend decreases with time; however, these symptoms are still prevalent years after diagnosis and treatment. Due the high prevalence, duration of symptoms, and the impact that these symptoms may have on cognitive function, depressive and anxiety symptoms were measured.

Cognitive limitations, particularly in the domains of learning and memory, are strongly associated with depression (Sun & Alkon, 2004). In addition, cognitive problems, in the form of concentration problems, are one of the criteria for a depressive episode (American Psychiatric Association, 2000). Some evidence suggests that factors impacting quality of life, such as menopausal symptoms and cancer-related fatigue, are not highly associated with cognitive function (Tchen et al., 2003). However, other studies suggest that long-standing symptoms of cancer-related fatigue, depression, and anxiety may impact cognitive functioning (Deimling, Bowman, Sterns, Wagner, & Kahana, 2006; Fan

et al., 2005b; NCCN, 2009; Roth, Geisser, Theisen-Goodvich, & Dixon, 2005; Valentine & Meyers, 2001). Furthermore, measures of distress may be significantly associated with perceived cognitive function (Schilling & Jenkins, 2007). For these reasons, depressive symptoms and cancer-related fatigue were measured and accounted for when assessing cognitive limitations in BCS.

Cognitive Limitations

Over two decades ago, research began addressing case studies of cognitive decrements experienced by cancer patients after chemotherapy which was termed “chemo brain” (Silberfarb, 1983). Since then, numerous studies have investigated cognitive functioning in a range of cancer survivors receiving different treatment regiments, with an emphasis on systemic chemotherapy.

Range of Cognitive Limitations. Cognitive limitations can range from subtle changes, such as consistently forgetting where one places one’s house keys, to impairments that can impact everyday function, such as inability to remember major events or tasks, difficulty organizing tasks, and attention deficits (Wefel, Witgert & Meyers, 2008). Shilling and Jenkins (2007) conducted interviews with 142 BCS and found that some of the common cognitive complaints included forgetting important tasks, names of people, appointments, parts of conversations, and personal events and experiencing concentration problems. Cognitive limitations can be described as global cognitive decrements; however, most studies have investigated cognitive limitations or decrements by measuring cognitive performance on several domains of cognitive functioning, such as attention, memory, language production (Green, Pakenham, & Gardiner, 2005).

This study investigated cognitive performance on several domains with the neuropsychological battery.

Cancer Treatment and Cognitive Limitation Studies. A meta-analysis of 30 neuropsychological studies investigating cognitive changes post-cancer treatment reported that decrements in executive function, verbal memory, and motor function were consistently found in cancer survivors (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003). Cross-sectional and longitudinal research has indicated that BCS treated with chemotherapy had more deficits in cognitive function than controls who have not received chemotherapy (Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Schagen et al., 1999; Tchen et al., 2003). While the magnitude of these decrements appeared to decrease with time, they persisted for many years in about 17 to 34 person of cancer survivors (Ahles & Saykin, 2002, 2007; Anderson-Hanley et al., 2003; van Dam et al., 1998).

Wieneke and Dienst (1995) investigated cognitive function in 28 BCS of working age (range 28 to 54 years old) who had undergone adjuvant CMF, CAF or a combination of these agents chemotherapy for three to 18 months. BCS were given a battery of neuropsychological tests and the results were compared to age, education, and gender-corrected published test norms. Cancer survivors scored significantly lower in memory, verbal fluency, abstract conceptualization, mental flexibility and speed of processing, attention and concentration, visuospatial ability, and motor function. Time since treatment, type of

chemotherapy, and depression were not significantly related to cognitive performance (Phillips & Bernhard, 2003,Wieneke & Dienst, 1995).

Schagen et al. (1999) found that deficits in concentration and memory were significantly more pronounced in axillary node-positive BCS who had received CMF chemotherapy and tamoxifen treatment, when assessed two years post-treatment, than cancer controls who had not received chemotherapy. There were no differences in cognitive performance between the chemotherapy with tamoxifen and the chemotherapy only group. Ninety-two percent of the survivors who underwent chemotherapy endorsed experiencing chemotherapy-induced menopause. This study indicated that tamoxifen did not add or alleviate cognitive impairment (Phillips & Bernhard, 2003; Schagen et al., 1999).

Schagen and colleagues (2002) investigated long-term effects in BCS receiving different types of chemotherapy (i.e., high dose CTC and FEC). This study found that all individuals reassessed four years post-treatment improved in cognitive function. However, the authors noted that some of the more severely cognitively impaired survivors at baseline did not participate in the four-year reassessment.

van Dam and colleagues (1998) found that BCS treated with high-dose (four cycles of FEC followed by single high dose of CTC and stem cell rescue) chemotherapy experienced significantly more cognitive impairment (32 percent) than cancer survivors treated with standard-dose (four cycles of FEC) chemotherapy (17 percent) and cancer survivors without chemotherapy exposure (nine percent). Eighty percent of the standard-dose and high-dose chemotherapy

survivors were taking tamoxifen during the time of the assessment. One hundred percent of the high-dose survivors and 94 percent of the standard-dose survivors experienced chemotherapy-induced menopause. High-dose chemotherapy cancer survivors scored 9.2 times lower than non-cancer controls on neuropsychological batteries. Cognitive impairment was of borderline significance when high-dose survivors were compared to standard-dose survivors. Regarding self-report measures, high-dose chemotherapy cancer survivors scored significantly lower than controls and standard-dose chemotherapy cancer survivors on physical function, role function, social function scales, and global quality of life. Self-reported cognitive function did not significantly differ between standard-dose and high-dose chemotherapy cancer survivors and these results were not significantly associated with anxiety, depression, or fatigue. This study provided some evidence for a dose response relationship between chemotherapy and cognitive decrements (Phillips & Bernhard, 2003; van Dam et al., 1998).

Brezden, Phillips, Abdolell, Bunston and Tannock (2000) conducted a cross-sectional study comparing cognitive performance of a cohort of breast cancer patients during chemotherapy treatment, a group of BCS who had completed chemotherapy treatment two years prior to the assessment, and a non-cancer control group. Breast cancer patients and BCS had significantly more overall cognitive limitations than the control group. The cancer patient group had significantly more decrements in the domains of memory and language than the control group. The cancer survivor group had better cognitive performance than

the cancer patients, suggesting an improvement in cognitive function with time. However, cancer survivors still had significantly more decrements in the domains of language and visual-motor skills than the non-cancer comparison group (NCCG). The groups did not significantly differ in mood states. This study supported previous findings that breast cancer patients experienced cognitive limitations, and these decrements were pervasive, as BCS, two years post-diagnosis, still experienced cognitive limitations (Brezden et al., 2000; Phillips & Bernhard, 2003).

Ahles and colleagues (2002) tested long-term (10 years post-diagnosis) BCS and lymphoma survivors, who had received either systemic CMF or FAC chemotherapy or local treatment (surgery, radiation therapy, or both) only, with neuropsychological batteries and self-report measures of depression, anxiety, and cancer-related fatigue. Although most cancer survivors scored within the normal performance range, the overall performance on neuropsychological batteries was significantly lower for the cancer survivors treated with chemotherapy than survivors without chemotherapy exposure. BCS with chemotherapy exposure scored significantly lower in the realm of psychomotor functioning and had self-reported lower scores in working memory. The study also indicated that only a subgroup of cancer survivors, 39 percent of survivors treated with chemotherapy and 14 percent of survivors treated with local therapy, experienced a decrement in cognitive performance. Survivors that received more cycles of chemotherapy had more cognitive deficits. Depression, anxiety, and cancer-related fatigue were within normal range and there were no significant

differences between the chemotherapy and local therapy groups. This study indicated that cognitive limitations experienced by cancer survivors may be subtle but persistent, as they are present years after diagnosis (Ahles et al., 2002; Phillips & Bernhard, 2003).

Castellon and colleagues (2004) compared cognitive function of BCS who received chemotherapy to BCS without chemotherapy exposure, and non-cancer controls. Eighteen (34 percent) of the BCS received chemotherapy and tamoxifen as their adjuvant treatment. A neuropsychological battery and self-reported measures of mood, energy level, and cognitive limitations were given. The study found that BCS with adjuvant chemotherapy performed worse on a global measure of cognitive function and in the domains of verbal learning, visuospatial functioning, and visual memory than BCS without adjuvant chemotherapy exposure. Women who were treated with chemotherapy and tamoxifen showed significantly more decrements in global functioning, verbal learning, visual memory, and visuospatial functioning than BCS treated with chemotherapy without tamoxifen. This study emphasized the importance of considering hormonal treatment when assessing for cognitive function. Self-reported cognitive limitations were related to depression scores, trait anxiety, and fatigue. This study found no relationship between perceived and observed measures of cognitive function and reported that perceived measures were influenced by mood and fatigue, highlighting the need to investigate the relationship between observed and perceived cognitive function in this population.

Ahles and colleagues (2008) compared neuropsychological performance and self-reported psychological tests of depression, anxiety, and cancer-related fatigue of invasive BCS, noninvasive BCS, and non-cancer controls. For the cancer patients, the first assessment was conducted post-surgical treatment and pre-adjuvant treatment (i.e., chemotherapy, radiation therapy, or hormonal therapy). The study found that the invasive BCS performed significantly lower than the non-cancer controls on reaction time, global measures of cognitive function, and rated themselves significantly higher on measures of depression, anxiety, and fatigue. Stage 0 BCS performed similarly to controls in neuropsychological tests. When comparing the performance of Stage I through III breast cancer patients to normative data (after adjusting the error rate by five percent), the study found that Stage I through III BCS were significantly more likely to be classified as having lower or impaired cognitive performance. Interestingly, this study indicated that observed cognitive limitations, in the form of reaction time, global cognitive function, and self-reported problems with fatigue, depression, and anxiety were present post-surgery and before exposure to chemotherapy and other forms of adjuvant therapy. Patients who were classified as having impaired cognitive performance did not significantly report higher perceived cognitive limitations. Indicating that after surgical treatment and prior to adjuvant chemically based treatments (e.g., chemotherapy, radiation therapy, hormonal therapy), breast cancer patients did not report perceived cognitive decline although some of the patients may have been classified as being cognitively impaired (Ahles et al., 2008).

Summary of Cognitive Limitations and Cancer Treatment Studies. Results of numerous studies involving neuropsychological testing have found decrements in a variety of cognitive domains in BCS. A meta-analysis of thirty neuropsychological studies investigating cognitive changes post-cancer treatment, reported that decrements in executive function, verbal memory, and motor function were consistently found in cancer survivors (Anderson-Hanley et al., 2003).

The studies on cognitive limitations have had certain limitations that impede the generalization of findings. For instance, many of the studies have had small sample sizes and may have been underpowered, did not have a control group, and did not account for possible confounders, such as chemotherapy-induced menopause (Phillips & Bernhard, 2003).

The evidence supporting the notion that cognitive limitations are associated with chemotherapy is strong, but not definitive. Donovan and colleagues (2005) did not find a difference in cognitive function between BCS who received adjuvant chemotherapy and BCS without adjuvant therapy. Other research has indicated that some cancer patients experience cognitive limitations after surgery but prior to being exposed to chemotherapy (Ahles et al., 2007). Wefel and colleagues (2004) found that 35 percent of BCS in their sample exhibited cognitive limitations, particularly with verbal learning, verbal memory, and one measure of psychomotor processing speed and attention, before being exposed to adjuvant cancer treatment. Wefel, Lenzi, Theriault, Davis and Meyers (2004) investigated cognitive function in BCS before chemotherapy (baseline),

approximately six months post-baseline (short-term assessment), and 18 months post-baseline (long-term assessment). Thirty-three percent of cancer survivors had cognitive impairment at baseline. Sixty-one percent of the participants declined in cognitive function between baseline and the short-term assessment. Of those that experienced decline, 45 percent improved in cognitive performance at long-term assessment. The remainder of survivors' performances remained impaired or results were mixed at long-term assessment.

These studies suggest that cognitive limitations persist in a subset of BCS after the acute survival stage. Although the etiology is not clear, treatment factors may cause or exacerbate pre-existing factors towards cognitive limitations. As a result, cancer treatment was measured in this study.

Possible Mechanisms for Cognitive Limitations. Research has begun to unravel the complexity of risk factors, protective factors and mechanisms behind cognitive limitations experienced after cancer. As discussed earlier in this paper, estrogen may have neuroprotective qualities on cognitive function (McEwen, 1999; Spencer, et al., 2008). Research has begun to identify possible risk factors for cognitive decline post-cancer that are associated with cancer treatment to include high chemotherapy dosage, multi-chemotherapy agents, intrathecal dispensation of chemotherapy, and use of adjuvant medications with neurotoxic effects (e.g., immunosuppressants, steroids, pain and anti-emetic medications). These same risk factors for cognitive decline may also contribute to other symptoms, such as fatigue and depressive symptoms which may be present for years after the cessation of treatment (Wefel, Witgert, & Meyers, 2008). In

addition, several pathways are being investigated as possible mechanisms for the expression of cognitive limitations in non-central nervous system cancer survivors (Ahles & Saykin, 2007; Wefel, Witgert, & Meyers, 2008). For example, studies have shown that long-term cognitive limitations were present in a subset of cancer survivors treated with chemotherapy even after accounting for the influence of cancer-related fatigue and psychological factors, suggesting the existence of an underlying biological influence (Ahles & Saykin, 2007).

Chemotherapy involves introducing toxins into the system that attack the cancerous cells. However, chemotherapy often has a systemic impact on the body as other cells in the body are also affected by these cytotoxins. Chemotherapy has been associated with a reduction in brain structures (e.g., frontal subcortical networks) and changes in metabolic pathways in frontal cortex and cerebellum (Saykin, Ahles, & McDonald, 2003; Saykin et al., 2006; Silverman et al., 2007; Wefel, Witgert & Meyers, 2008). In addition, tamoxifen and chemotherapy have been associated with decreased metabolism of the basal ganglia (Silverman et al., 2007). While the exact mechanism by which cognitive limitations occur in cancer survivors is still under investigation, several biological pathways involving the effects of chemotherapy on changes in brain structure have been proposed. A review by Ahles and Saykin (2007) outlined these proposed biological mechanisms of cognitive limitations, which include ability of chemotherapy agents to cross the integrity of the blood brain barrier, deregulate the immune system, damage DNA, lead to genetic susceptibility, and decrease hormone levels that may have neuroprotective qualities.

Crossing the Blood Brain Barrier. Recent evidence suggests that small doses of chemotherapy agents may be able to cross the blood brain barrier. This may be due to genetic variability of the multidrug resistance one gene (MDR1), which encodes the P-glycoprotein (P-gp), a protein that affects drug uptake into the brain. Normally, P-gp transports chemotherapy agents out of the brain. However, several mutations may cause the blood brain barrier transporters to pump lesser amounts of the chemotherapy agent out of the brain. Although the remaining amount of chemotherapy agents in the brain may not be enough to exhibit severe cytotoxic properties, these chemicals may cause some cell death and impair normal mitotic activity in the brain (Ahles & Saykin, 2007; Hoffmeyer et al., 2000). A recent study by Han and colleagues (2008) investigated the effect of one commonly used chemotherapy agent, 5-fluorouracil (5-FU), on in vivo and in vitro brain structures (Han et al., 2008). The study found that 5-FU was associated with cell death of non-dividing oligodendrocytes, as well as cell division suppression in dividing neurons, and these changes had the potential to have a clinical impact on cognitive function. The Han et al. (2008) study also found that the systemic administration of 5-FU had delayed degenerative effects on white matter. Hence, a single chemotherapy agent could have short-term and long-term effects on brain structures (Han et al., 2008).

Neuroimaging and neurophysiological studies have indicated that there is a change in brain activity/function in cancer survivors who expressed cognitive difficulties. For example, Inagaki et al. (2007) found that BCS who had chemotherapy one-year prior to the assessment, had smaller white and gray

matter volume than controls and this structural difference correlated with poorer neuropsychological performance. A study using water positron emission tomography (PET) found that long-term BCS survivors (5 to 10 years post-chemotherapy) had different activation patterns than BCS who had not been treated with chemotherapy (Silverman et al., 2006). More neuroimaging and neurophysiological studies are needed to further elucidate the effects of cancer treatment on brain structure and function (Wefel, Witgert, & Meyer, 2008).

A rat study conducted by MacLeod and colleagues (2007) found that specific chemotherapy agents, cyclophosphamide and doxorubicin slowed down freezing behaviors during a training environment exercise. Chemotherapy agents did not have an effect on cue-specific fear to a tone. These results suggest that the hippocampus may be sensitive to the effects of these chemotherapy agents. Cell death, synaptic reorganization in the hippocampus, or both phenomenon may manifest in specific learning decrements or impaired memory (MacLeod et al., 2007).

DNA Damage. Chemotherapy agents may increase levels of non-protein bound iron and free radicals that are associated with reduced antioxidant capacity and increased oxidative stress, which commonly causes single- or double-strand breaks in mitochondrial DNA in neurons and peripheral blood lymphocytes. Furthermore, chemotherapy may decrease telomere length in the DNA replication process of mitotic cells, such as glial cells. These factors may lead to DNA damage results in cell aging and apoptosis (Ahles et al., 2007; Wefel, Witgert, & Meyer, 2008).

Genetic Susceptibility. Although not fully understood, some evidence suggests that BCS have experienced higher cognitive limitations prior to engaging in cancer treatment (Ahles et al., 2007; Wefel et al., 2004; Wefel, Witgert & Meyers, 2008). It is thought that DNA damage associated with mutations or other biological processes that prevents cell repair may lead to cognitive deficits and may also be a risk factor for the development of cancers. Hence, this line of thinking suggests that individuals with this predisposition for DNA damage may be at risk for developing cancer and cognitive limitations, and these cognitive limitations may be exacerbated or retained by chemotherapy exposure (Ahles & Saykin, 2007).

Immune System Deregulation. Cytokines are thought to play an important role in cognitive function, as cytokines affects neuronal and glial functioning and repair, and regulation of dopamine and serotonin. Cytokines and the inflammatory response has been associated with the development of certain cancers (e.g., cervical, ovarian), and cytokine deregulation is thought to negatively impact cognitive function (Wilson, Finch, & Cohen, 2002). Cancer patients have high levels of peripheral cytokines prior to cancer treatment. These data suggest that there may be a link between this immune response, cancer, and cognitive decrements even before the introduction of chemotherapy. However, the introduction of cytotoxic agents may increase these negative effects on cognitive function. Cytotoxic chemicals attack cells and illicit the immune system response to include an increase in pro-inflammatory cytokines (Ahles & Saykin, 2007; Wilson et al., 2002). Chemotherapy may lead to cytokine

deregulation, which leads to oxidative stress and DNA damage. This may lead to a perpetuating cycle where the damaged DNA leads to an overactive cytokine release, leading to more oxidative stress. Genetic polymorphisms may also increase cytokine deregulation, as seen in some patients with depression and Alzheimer's disease (Tonelli, Postolache, & Sternberg, 2005). Some studies have indicated that long-term cancer survivors with higher levels of peripheral cytokine levels have significant decrements in cognitive functioning (e.g., information processing speed, executive function, reaction time, spatial ability). Increases in pro-inflammatory cytokine levels have been associated with decrements in cognitive performance, fatigue and quality of life measures for cancer patients. However, no causal relationship between cytokine deregulation and cognitive function has been established and this relationship requires more investigation (Ahles & Saykin, 2007; Cleeland et al., 2003; Meyers et al., 2005; Wefel, Witgert & Meyers, 2008; Wilson et al., 2002).

Decrease in Neuroprotective Proteins and Hormones. Other proposed mechanisms involve the influence of genetics on neural repair and neurotransmission. Apoliprotein E (APOE), a "complex glycolipoprotein that assists in the uptake, transport and distribution of lipids" (Ahles & Saykin, 2007, p. 198), may be essential for repair and plasticity of neurons (Ahles et al., 2003). Long term cancer survivors who have a specific genotype consisting of the main allele E4 on chromosome 19 of APOE have been found to have lower performance on executive functioning, visual memory, and spatial ability (Ahles et al., 2003; Laws et al., 2002). It is hypothesized that the E4 allele of APOE may

be less effective at neuronal repair and neuronal growth than other genotypes. Also, it may be that individuals with the E4 genotype might have morphological variations in brain structures, such as lower volume of the hippocampus which is responsible for memory (Ahles & Saykin, 2007). Brain-derived neurotrophic factor (BDNF) is a protein found mainly in the prefrontal cortex and hippocampus in the brain, as well as the periphery, that assists in cell repair (Savitz, Solms, & Ramesar, 2006). BDNF assists in the repair and survival of neurons, as well as dendritic and axonal growth and improved functioning of synapse. A polymorphism of BDNF involving valine-to-methionine amino-acid substitution at codon 66 (Val66Met) has been associated with reduced hippocampal volume and lower performance on memory and executive function tasks. Although there is some evidence supporting the impact of BDNF on cognitive functioning, the relationship between BDNF polymorphism and chemotherapy has not been investigated (Ahles & Saykin, 2007; Savitz et al., 2006).

Catechol-O-methyltransferase (COMT) is an enzyme involved in the metabolic deactivation of catecholamine neurotransmitters by methylation of dopamine and noradrenaline (Savitz et al., 2006). COMT is essential for dopamine regulation in the frontal cortex. A common polymorphism involves an amino-acid substitution, where a valine changes to a methionine. Individuals who have more expression of the valine amino acid on COMT will metabolize dopamine quicker, which will result in a decreased concentration of dopamine. Lower dopamine levels in the frontal cortex have been associated with poorer performance on executive function and memory tasks in individuals without

cancer (Ahles & Saykin, 2007; Savitz et al., 2006). Unpublished data from Ahles and Saykin have found that breast cancer and lymphoma survivors treated with chemotherapy with the COMT valine allele scored significantly lower in the realms of verbal memory and spatial ability (Ahles & Saykin, 2007). This data suggests that cancer survivors treated with chemotherapy with the valine allele will experience decrements in cognitive performances before treatment, which may become more pronounced after chemotherapy (Ahles & Saykin, 2007).

Adjuvant breast cancer therapies, such as chemotherapy and tamoxifen, are associated with amenorrhea and ovarian ablation (Clarke et al., 2005; Goodwin et al., 1999; Stearns et al., 2006). Decreased estrogen, as experienced during menopause, has been associated with decrements in hippocampal and frontal lobe tasks, such as working memory (Maki, Gast, Vieweg, Burriss, & Yaffe, 2007). Although the cognitive effects of chemotherapy induced menopause has not been well studied, it is possible that the sudden decrease in estrogen may have a significant impact on cognitive and emotional functioning of female cancer survivors (Ahles & Saykin, 2007).

In sum, mechanisms involving chemicals related to chemotherapy crossing of the blood brain barrier, causing DNA damage, immune system deregulation, or decreasing neuroprotective proteins and hormones in the body have been proposed to explain the association between breast cancer and cognitive limitations. These proposed mechanisms elucidate the complexity and several pathways that may influence changes in cognitive function and brain structure following cancer treatment (Ahles & Saykin, 2007). The complexity of

the biological pathways highlights reasons for the variation in severity, persistence, and type of cognitive limitations experienced by a subgroup of cancer survivors.

Measurement of Cognitive Limitations

Measurement in Medical Population. Several studies that have assessed measurement of cognitive function in a variety of medical populations have indicated differences between self-reported and behavioral observations of cognitive functioning. In addition, several studies have found that people of varying medical conditions or status (e.g., multiple sclerosis, chronic fatigue, older and younger patients at a memory clinic, and people undergoing surgery) who experienced higher self-reported cognitive difficulties were more likely to have emotional difficulties (Derouesne, Lacomblez, Thibault, & LePoncin, 1999; Maor, Olmer, & Mozes, 2001; Moller et al., 1998; Short, McCabe, & Tooley, 2002). Wong and colleagues (2006) found that individuals with questionable dementia and mild Alzheimer's disease reported high frequency of subjective memory problems; however, Alzheimer patients were more likely to overestimate their neurocognitive performance. The study also highlighted that the presence of depressive symptoms may also affect subjective memory complaints in this population. Tierney, Szalai, Snow and Fisher (1996) found that depression was correlated with self-reported cognitive limitations, but not observable "objective" measures of cognitive function in patients with non-dementia associated memory problems. Roth, Geisser, Theisen-Goodvich, and Dixon (2005) found that depressive symptoms and fatigue significantly accounted for self-reported

cognitive complaints in women with chronic pain. These studies emphasize that perceived and observed cognitive limitations may be concordant. In addition, diverse factors (e.g., depressive symptoms, fatigue) may differentially impact the measurement of cognitive limitations in medical populations, to include BCS (Wefel, Witgert & Meyers, 2008).

However, some data has indicated that the measurement of perceived and observed cognitive limitations is more congruent than the previously described studies had suggested. Clarnette, Almeida, Forstl, Paton, and Martins (2001) investigated the relationship between neurocognitive tests of memory and self-reported memory deficits with healthy volunteers who had some memory complaints, without having a history of dementia, stroke, or severe cognitive deficits. The study found that neuropsychological measures of memory loss were independently associated with self-reported decrements in memory ($p=0.002$). Ownsworth and McFarland (1999) used two self-report measures, the Self-Reported Memory Problems (SRMPS) measure and the Daily Memory Problems (DMPS) checklist, and two neuropsychological measures of cognitive function, the Rivermead Behavioural Memory Test (RBMT) and the Wechsler Memory Scale-Revised (WMS-R), to measure cognitive performance in long-term (15 years) acquired brain injury patients. This study found that both self-reported measures of memory functioning were significantly correlated with each other ($r=0.69$; $p=0.01$) and with the RBMT ($r=0.52$, $p=0.05$ for the SRMPS and $r=0.57$, $p=0.01$ for the DMPS). However, only one of the self-reported measures was significantly and moderately correlated with the WMS-R ($r= 0.52$; $p=0.05$ with the

DMPS). The relationship between self-reported and observed cognitive function is complex, as perceived measures of the extent of cognitive change may measure a different dimension of cognitive function from observable measures of cognitive limitations (Poppelreuter et al., 2004). Therefore, evaluating different perceived and observable measures as they pertain to neurocognitive assessments remains a critical concern, especially in terms of a major outcome such as work productivity or work limitations.

Measurement in Cancer Survivors. Cognitive limitations in cancer survivors have been documented to be diffuse, sometimes subtle, and often long lasting (Ahles et al., 2007). The variety of symptom type, severity, and duration makes measurement of these symptoms complex. Cognitive function is usually evaluated through self-report measures, neuropsychological testing or both. Neuropsychological testing is considered the gold standard for measuring cognitive function (Tannock et al., 2004). However, neuropsychological batteries are lengthy, manpower intensive, expensive, and may take the participant away from work and other daily activities for many hours or days. While neuropsychological batteries provide detailed information of various domains of cognitive functioning, it is unclear how these more specific results relate to the cancer survivor's daily functioning and work. The degree to which self-report measures of cognitive limitations relate to work functioning, when accounting for confounders such as mood state, is unclear. We previously reported that self-reported cognitive limitations experienced after the cancer experience significantly contributes to the variance in self-reported work limitations

(Feuerstein, Hansen, Calvio, Johnson, & Ronquillo, 2007). However, the relationship between the more detailed neuropsychological function obtained from standard neuropsychological evaluation and self-reported work limitations is currently unknown. Cancer survivors have a major impact on the work force, and cognitive decrements can be associated with work productivity (Feuerstein et al., 2007). Decrements in work productivity can lead to significant financial burden to employers (Goetzel et al., 2004) and to many frustrations on the part of the cancer survivor, so primary and secondary prevention efforts may be warranted. As an initial step to the development of such interventions, it is important to determine whether various assessment approaches of cognitive function accurately detect problems at work.

Several studies are showing a disconnect between perceived and observed measures of cognitive function in cancer survivors. Poppelreuter and colleagues (2004) administered a neuropsychological battery and several self-report measures of cognitive functioning to 119 cancer patients of various types of cancers, of which 24 percent met the study's criteria for cognitive impairment (below the tenth percentile in at least two domains of cognitive function). The study found non-existent or small correlations between neuropsychological battery and the self-report measures (range of correlations between $r = -0.01$ and 0.24). The cancer survivor literature has found similar trends between perceived and observable measures of cognitive function as seen in other medical populations, indicating that this incongruence between measures is prevalent.

Measurement in Breast Cancer Survivors. Research with BCS mirrors what has been found with different cancer survivor groups. Mehnert et al. (2007) found that most of the neuropsychological tests employed in a study investigating cognitive function of 47 long-term BCS did not correlate with perceived measures of cognitive function. However, in this study, Digit Span Forward Test (measure of working memory) was significantly correlated with perceived overall cognitive impairment and Digit Span Backwards (measure of working memory and cognitive flexibility) was moderately correlated with perceived overall cognitive impairment. Vardy and colleagues (2006) found no correlation between electronic neuropsychological probes and subjective cognitive limitations (range of r= 0.05 to -0.07) in cancer survivors. Although the sample had different cancer types, 94 percent of the sample consisted of female BCS. Castellon and colleagues (2004) also found no relationship between neuropsychological batteries and self-reported measures of cognitive function in a breast cancer survivor sample. Ahles and colleagues (2002) found small and non-significant correlations between self-reported cognitive limitations in the domains of learning, working memory, attention and concentration, and remote memory with neuropsychological testing results in breast cancer and lymphoma survivors. These studies highlight a disconnect between the two key methods of measuring cognitive function in the cancer survivor population, particularly in BCS (Wefel, Witgert & Meyers, 2008).

Several factors may contribute to objective and subjective cognitive limitations in cancer survivors, such as cancer treatment/history, psychosocial

factors, physical health, and emotional health (Green et al., 2005). For BCS, there is evidence that demographics, type of adjuvant cancer treatment received, menopausal status, stress, cancer-related fatigue, depressive symptoms, and anxiety may impact perceived measures of cognitive function, and observed measures of cognitive function (Ahles et al., 2002; Ahles et al., 2007; Brezden et al., 2000; Castellon et al., 2004; Mehnert et al., 2007; Schagen et al., 2001; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Wefel, Witgert & Meyers, 2008). As a result, these possible confounders were accounted for in the current study.

While perceived and observed cognitive limitations would conceptually be variants of the same construct, the differences may lie in the inherent nature of the measures. For instance, a breast cancer survivor completing a self-report measure may compare their current function to their pre-morbid function. On the other hand, the results of a cancer survivor's neuropsychological battery may be compared to norms from the general population, which may not accurately portray pre- and post-disease functioning for that individual (Poppelreuter et al., 2004). In this case, perceived measures may be more accurate in portraying changes in cognitive function and consequent impact in other realms of functioning, such as work. As a result of this possibility, there is a need to compare the "gold standard" of neuropsychological testing to self-report measures against another realm of functioning, such as work productivity and work limitations. Investigating the relationship between cognitive measures as they relate to work can assist primary care providers and other health providers

of diverse specialties to develop more effective approaches to this important outcome to cancer survivors.

Work

Burden of Cancer on Work Productivity. Cancer has been identified in the top 20 physical health conditions that impact productivity and cost burden to the work force (Goetzel et al., 2004). Cancer has been associated with as high as 14.6 percent productivity loss due to absenteeism, or missed work days, and 15 percent productivity loss due to presenteeism, or working at a reduced capacity (Goetzel et al., 2004).

The burden of cancer due to lost productivity and indirect costs was estimated to be $15.5 billion for the year 2003 (Chang et al., 2004) and $18.2 billion for 2008 (ACS, 2008). Yabroff, Lawrence, Clauser, Davis and Brown (2004) conducted a study of 1,823 cancer survivors from the 2000 National Health Interview Study (NHIS). Cancer survivors reported statistically significantly poorer health across every measure of utility, work productivity, and general health. The study also found that long term survivors continued to significantly experience burden at work in that 11 years post-diagnosis reported an average of 53.8 days lost from work were observed in12 months, compared to 27.5 days reported by the matched non-cancer control group. Cancer survivors reported significantly experiencing losses in productivity due to being unable to work due to health problems and being limited in amount or kind of work because of health problems. BCS reported an average of 43.4 days lost from work in one year, compared to 23.6 days by the NCCG. Amongst BCS, 27.5 percent significantly reported fair or poor health status, compared to 17.9 percent of the non-cancer

group. Additionally, 14.4 percent of BCS significantly reported spending greater than 10 days in bed in one year, compared to 7.7 percent of the non-cancer group. Cancer survivors continue to experience significant and indirect burden of illness at work years post-diagnosis (Yabroff et al., 2004).

Breast Cancer and Work. As one of the largest cancer survivor groups, breast cancer survivor's absence or decrement in performance at work would greatly impact employers. Breast cancer patients return to work at high rates and often face challenges that may decrease their productivity (Bradley & Bednarek, 2002). It is important to accurately measure these limitations as they relate to work functioning and implement appropriate interventions.

Approximately 40 percent of cancer patients within the U.S. are working age (Short, Vasey, & Belue, 2007). BCS tend to be a younger cohort than overall cancer survivors, as 60.9 percent of BCS are diagnosed before the age of 65 (ACS, 2007). Many breast cancer patients worked prior to diagnosis and continue to work during their cancer treatment (Bradley & Bednarek, 2002). However, BCS who work during treatment face many challenges that impact their work productivity and may increase absenteeism. BCS, who continue to work, miss an average of 44.5 days of work during cancer treatment (Bradley, Oberst, & Schenk, 2006). Bradley and Bednarek (2002) found that approximately 88 percent of BCS who worked pre-diagnosis continued to work six months post-cancer diagnosis. Other studies have estimated that between 79 and 80 percent of BCS returned to work or continued to work at 12 months and three years post-cancer diagnosis (Bouknight et al., 2006; Maunsell et al., 2004). A qualitative

study of cancer survivors found that reasons for high rates of return-to-work included financial pressures, a way to regain a sense of normality, work served as an indicator of physical health, and feeling loyalty to work (Kennedy et al., 2007) .

The majority of BCS are employed years post-cancer. Maunsell and colleagues (2004) found that BCS who worked three years post-diagnosis earned significantly more money than their pre-diagnosis income, indicating significant financial benefits to returning to work. Returning to work with a chronic illness, such as cancer, can be beneficial to the mental health of the individual, and yet, it has been associated with decrements in work productivity (Wang et al., 2003). Bowen and colleagues (2007) found that working BCS reported better physical function than BCS who were unemployed, retired, or disabled. These studies indicate that BCS continue to work or return to work soon after diagnosis and continue to work years after diagnosis, which has financial benefits for the breast cancer survivor.

Returning to work has been associated with improvements in quality of life for cancer survivors through increased social networks, improved self-esteem, and monetary stability (Spelten et al., 2003). However, BCS face many changes (e.g., cancer-related fatigue, depressive symptoms, and cognitive changes) that may impact their ability to return-to-work and their productivity (Bradley & Bednarek, 2002; Spelten et al., 2003).

Chemotherapy treatment, axillary node dissection, and high job demand/job stress were associated with not returning-to-work ten-months post-

primary surgical treatment in early stage BCS (Johnsson, et al., 2009). Another recent study investigating factors that contributed to not returning-to-work in recurrence-free early-stage pre-menopausal BCS two -years post-treatment indicated that chemotherapy and adjuvant endocrine therapy (e.g., Tamoxifen, Tamoxifen in combination with other hormone therapy Goserelin, Goserelin alone) were significantly associated with not returning-to-work (Johnsson, et al., 2007). Radiation therapy and demographic factors (e.g., age, marital status) was not associated with return-to-work in this sample. The most common self-reported reasons for women not returning-to-work two years-post treatment were due to the job environment, the nature of their pre-cancer employment (e.g., physically demanding, non-supportive environment), and feeling physically fatigued (Johnsson, et al., 2007). Kennedy et al. (2007) found that survivors who had less job stress, flexibility, accommodations and support at work were likely to have a better experience in returning to work and feel more productive. As a result, it is important to measure occupational factors that may impact work productivity.

A qualitative study by Kennedy and colleagues (2007) investigated the experience of work after cancer with a sample of 29 cancer survivors (to include breast cancer) 1 to 10 years post-diagnosis. Approximately 25 percent of this cohort indicated that they had no problems adjusting to their job after cancer. However, several survivors indicated experiencing several negative factors that made the transition to work difficult. For example, several survivors in this study reported having difficulties with feeling stressed out, coping and concentrating at

their jobs when they returned to work. Approximately one-third of participants indicated that they felt their employers or coworkers had high expectations of them upon returning to work. Many of the survivors mentioned having unrealistic expectations for themselves and forgetting that they needed time to recover and heal. Some survivors indicated that particularly early on, they had to take time off for medical care, and this added pressure and worry about impacting their performance at work. Finally, the majority of survivors indicated that several side effects of cancer and treatment made it very difficult to adjust to their work environment. In particular, fatigue and tiredness were highlighted as the most frequent and long-standing disruptive side effects at work (Kennedy et al., 2007).

Cancer-related fatigue is commonly experienced after cancer treatment and can be persistent for years. Cancer-related fatigue has been significantly associated with survivor's decreased ability to return-to-work and work performance (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007; Mock, 1998; Spelten et al., 2003). Studies have shown that up to 50 percent of BCS experience clinical depression, anxiety, or both within the first year post-cancer diagnosis (Burgess et al., 2005; Hofman et al., 2007; Mock, 1998; Spelten et al., 2003). Lavigne and colleagues (2008) found that after accounting for breast cancer stage, fatigue and hot flushes were associated with work limitations in a group of 83 BCS. This study found marriage and higher personally earned income to be protective factors in work productivity for BCS. A longitudinal observational study with 222 BCS found that the prevalence of depression and anxiety in BCS decreased to 25 percent during the second year

post-cancer diagnosis, and 15 percent by the fifth year post-diagnosis (Burgess et al., 2005). Arndt and colleagues (2004) reported that nearly 90 percent of 314 BCS reported feelings of depression, irritability, tension, or worry one year post-diagnosis. Limitations in emotional and cognitive functioning were more pronounced in the younger than the older survivors, as compared to general female population norms. A few studies have reported that depression is negatively associated with quality of life, including work performance in BCS (Arndt et al., 2004; Reich et al., 2007). As a result, the impact of depression and cancer-related fatigue should be considered when investigating work productivity in BCS.

Cognitive limitations have been associated with work productivity in brain and BCS (Feuerstein et al., 2007; Hansen et al., 2008; Wefel et al., 2004). Wefel and colleagues (2004) found that cancer survivors that experienced cognitive limitations had greater self-reported difficulties at work than cancer survivors not experiencing cognitive decline. As a result, cognitive limitations at work need to be further understood, while accounting for confounding factors like depression and fatigue.

Ethics and Internet-based Research

There are advantages, as well as unique ethical considerations to consider when designing an Internet study. The advantages include: the ability to extend access to participants across a wide geographical range; the ability to obtain participation from hard to reach populations; and increased ability to obtain a research sample that is more demographically diverse. Other

advantages for the researcher include savings in cost and time from travel and venue hire (location and time for interviewing participants), ease of data collection, and increasing ease of administration and burden for participants, as participants can take the survey in the environment of their choosing (Mann & Stewart, 2000). Valaitis and colleagues (2005) and Joinson (1999) found that conducting research via the medium of the Internet increases the feeling of anonymity and disclosure and decreases embarrassment for participants. Hence, Internet research may increase the accuracy of the data.

In light of these advantages, consideration must be paid to ethical constraints, such as security, the possibility of sampling biases and validity of the online data (Whitehead, 2007). In order to ensure security of personal information, we only used encrypted and HIPAA compliant websites. Data was stored in password protected computers in locked offices at the Uniformed Services University.

It has been suggested that individuals who access the Internet, particularly for health related materials, consist of a homogenous cohort of middle-to-upper class Caucasian and younger individuals. This cohort effect could lead to a sampling bias in which older individuals, lower class, and minorities may be less represented. Lorence, Park and Fox (2006) found that ethnic minorities, particularly Hispanics, represent the “digitally underserved groups” and access the Internet for health related information to a lesser extent than their Caucasian counterparts. However, when comparing Internet health information access from 2000 to 2002, the gap between ethnic and racial minorities and Caucasians

decreased. This indicates that although the ethnic/racial minority divide still exists, minorities have increased their time accessing online health information over recent years. Recent data suggests that ethnic/racial minorities and members of traditionally marginalized groups, such as the gay, lesbian, bisexual, and transgender (GLBT) community, as well as older individuals are increasingly accessing the Internet for health related information (Lorence et al., 2006; Mann & Stewart, 2000; Whitehead, 2007). As the United States population is increasingly becoming Internet savvy with regards to health information, the probability of sampling bias decreases. Studies also indicate that Internet studies, particularly with larger sample sizes, obtain participants that are more demographically diverse than in studies conducted through normal means (Mann & Stewart, 2000; Whitehead, 2007).

Use of the Internet with cancer survivors and their families is increasing. Pereira, Koshi, Hanson, Bruera, and Mackey (2000) found that approximately 47 percent of the BCS surveyed had Internet access and routinely used their access for cancer related topics. However, 33 percent of the BCS surveyed reported that they were unfamiliar with the Internet. BCS who accessed the Internet for cancer related topics were significantly younger and better educated than BCS who did not access the Internet (Pereira et al., 2000). A more recent study (Simon & Schramm, 2008) reported that 76 percent of cancer patients of varying ages and their families accessed the Internet for cancer related information.

These data indicate that although a sampling bias might still exist when conducting an online study; the sampling bias might not be as large as expected.

To mitigate some of the possible sampling bias, we targeted much of our recruitment to breast cancer survivorship web sites, including those sites that cater to ethnic/racial minorities and other minority groups. Furthermore, we recruited by several avenues besides the Internet, including flyers at hospitals, support groups, and newspaper ads.

Another ethical consideration is regarding the credibility and validity of the data. There is the possibility that individuals may misrepresent themselves online. A review of the literature (Whitehead, 2007) concluded that very little research had been conducted on this issue, and detection of bogus representation is difficult. However, Buchanan (2005) reviewed their online study for fraudulent submission and excluded only one participant from 1199 participants (less than one percent). The review concluded that fraudulent representation on online studies is hard to detect, yet highly unlikely (Whitehead, 2007). Despite the low probability, the authors of this study wished to decrease the possibility of bogus data by adding questions to the screener inquiring more details about the participant's cancer diagnosis and treatment. This will allowed the researchers to screen for inconsistencies. Also, monetary compensation was not provided. Instead, participants were compensated for their time with their choice of either a stress relaxation workbook or a book on cancer survivorship.

Methods

Study Rationale and Hypotheses

The majority of BCS are within working age and with increased screenings and improvements in medical technology, prognosis for most breast cancers is

good. As a result, the breast cancer survivor community is a growing population, particularly within the workforce. Many BCS have been treated with surgeries, radiation therapy, aggressive adjuvant therapies, such as chemotherapy, estrogen receptor modulators, monoclonal antibodies, aromatase inhibitors, or a combination of therapies. These aggressive treatments have many short-term and long-term side effects. One of the long-term effects commonly seen in up to 34 percent of BCS are cognitive limitations, which vary in type and magnitude of cognitive decrements (Ahles & Saykin, 2007). Cognitive impairment can have a negative impact on quality of life, including work limitations (O'Shaughnessy, 2003). Work limitations are of interest to occupational and medical specialists, the cancer survivor, and employer, due to both financial, health, and productivity implications. Decrements in work productivity can be costly to employers and to survivors (Maunsell et al., 2004; Spelten et al., 2003).

Currently, there are two modalities used in measuring cognitive function, self-report and neuropsychological batteries. However, it is unclear how or if the two modalities of measurement relate to each other. In addition, the relationship between the two modalities of measurement and work limitations is also unclear. Investigating the independent contributions and the relationship of self-reported and observed cognitive limitations is important. As more BCS are returning to work or experience the long-term effects of the cancer or cancer treatment, it would be beneficial to efficiently, effectively, and validly measure their cognitive function, particularly as they pertain to work.

Proposed conceptual model. In this study, we focused on the relationship between cognitive impairment and work limitations. The conceptual model proposed in this study (Figure 1) separates cognitive limitations into perceived and observed cognitive limitations to distinguish the limited relationship that has been historically observed between the two types of measurements as reviewed in previous sections. Factors impacting cognitive limitations have been grouped into demographics (race, ethnicity, age, education), health history (cancer treatment, menopausal status), and emotional and physical health factors (depressive symptoms, anxiety symptoms, physical fatigue, pain, distress, job stress). The outcome of interest is work limitations. Studies have shown that individuals who reported cognitive decline after cancer also reported more work limitations (e.g., inability to organize their tasks at work, forgetting work tasks; Wefel, Witgert & Meyers, 2008). This study tested the association of the above factors with work limitations.

Aims and Hypotheses

Aim 1. The first aim was to investigate the factors that impact work limitations in BCS and NCCG. This aim investigated possible differences in factors that independently and significantly contribute to work limitations in the breast cancer survivor group and NCCG. This aim sought to replicate what has been found in a previous study (Hansen, et al., 2008), where fatigue significantly contributed to work limitations in BCS; while depressive symptoms significantly contributed to non-cancer survivors. Based on our conceptual model, we anticipated that the relationship between cognitive limitations and work

productivity is strong and direct, regardless of whether or not the individual has had cancer. However, one of the factors that impact cognitive limitations is health history and emotional and physical health. As a result, we anticipated that cognitive limitations will be higher in BCS, due to factors related to the cancer experience, which will result in higher work limitations. We speculate that pronounced decrements in functioning will strengthen the correlation between perceived cognitive limitations and work productivity. Behavioral measures may detect very subtle cognitive limitations experienced by a breast cancer survivor. However, it is possible that very subtle limitations in performance tests may not be associated with perceived functioning at work. Our research group found that self-reported cognitive limitations significantly and independently contributed to work limitations in brain tumor survivors (Feuerstein et al., 2007). Although brain tumor survivors endure a different disease and treatment regiment than BCS, they have some factors in common, such as the psychological distress that may come with a cancer diagnosis and the introduction of cytotoxins into the body to fight cancer. As a result, it may be possible that similar to brain tumor survivors, for BCS, perception of cognitive limitations may also have a strong relationship with work limitations. It is also possible that this relationship may be present regardless of cancer history. As a result, perceived cognitive limitations may be more strongly associated with work limitations with both BCS and people who have not had breast cancer. The hypothesis for this aim was as follows:

Hypothesis 1. Perceived cognitive limitations will contribute to work limitations to a greater degree than observed cognitive limitations in both groups

accounting for demographic, medical history, occupational characteristics, and symptom burden (depressive and anxiety symptoms, fatigue).

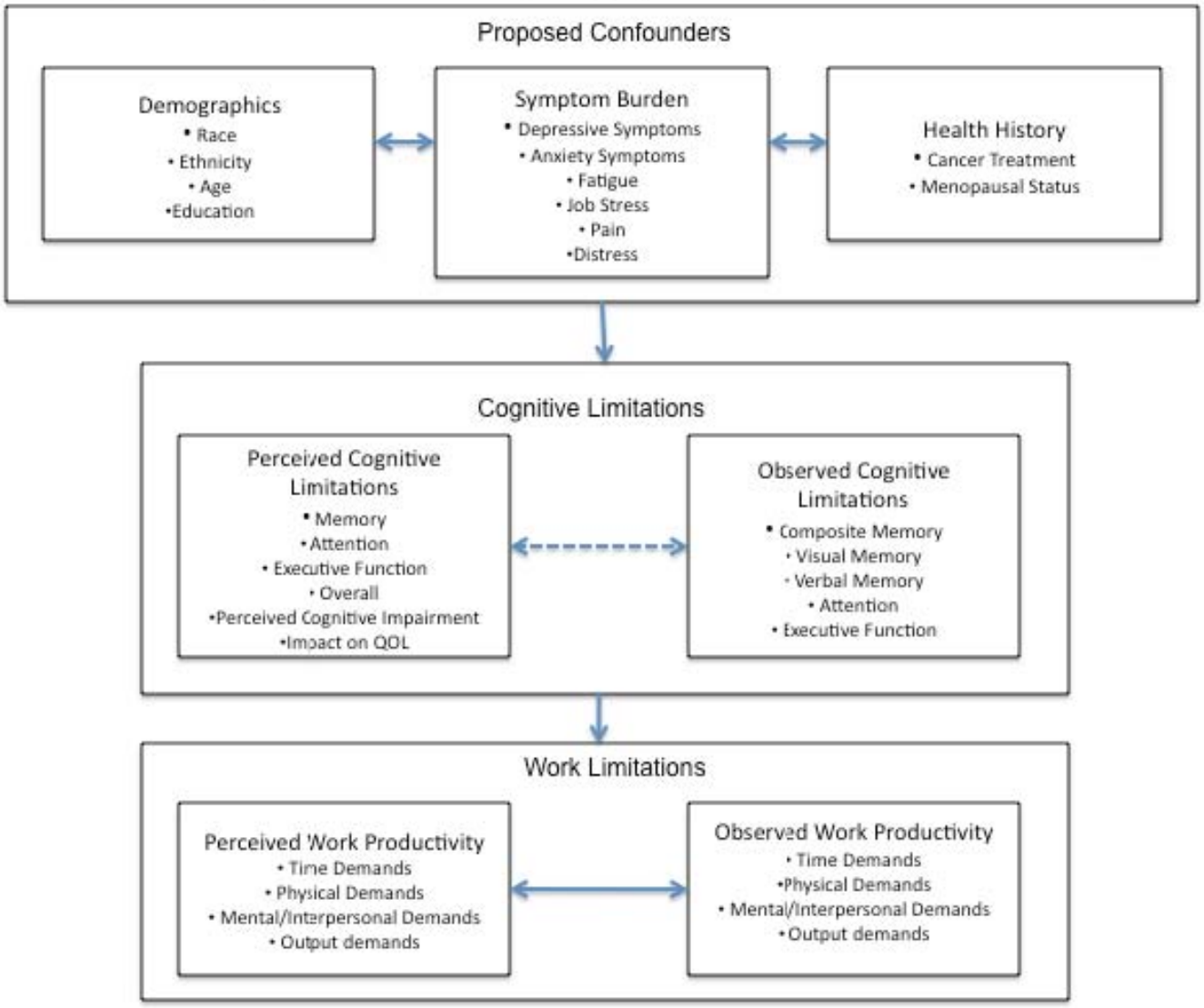
Hypothesis 1a. There will be a stronger relationship between fatigue and work limitations in breast cancer while there will be a stronger relationship between depressive symptoms and work limitations in the NCCG (based on our previous work).

Aim 2. The second aim was to investigate the relationship between perceived (self-reported) and observed (computerized neuropsychological testing) measures of cognitive limitations, accounting for demographics, fatigue, and mood in BCS and a NCCG as it pertains to work limitations. Group differences in the expression of fatigue, depressive and anxiety symptoms, and cognitive limitations will give us a better idea of the symptom burden of the cancer experience. This assessment allowed us to compare our results to that of other studies, which have mainly found decrements in different dimensions of cognitive limitations in cancer survivors when compared to non-cancer controls (Anderson-Hanley et al., 2003; Brezden et al., 2000; Wefel, Witgert, & Meyers, 2008). The relationship between perceived and observed measures of cognitive function was also investigated. The majority of the literature has found no or a small relationship between both modalities of measurement (Ahles et al., 2002; Castellon et al., 2004; Poppelreuter et al., 2004; Vardy et al., 2006) and we anticipate finding the same trends. This would support the notion that the self-report and neuropsychological probe measure different aspects of cognitive function (Poppelreuter et al., 2004).

Hypothesis 2. BCS will endorse greater symptom burden (depressive and anxiety symptoms, fatigue, and cognitive limitations) than the NCCG.

Hypothesis 3. The relationship between observed and perceived cognitive limitation measures will be significantly different.

Figure 1. Conceptual Model – Factors impacting cognitive limitations and work limitations in BCS



General Overview

Perceived and observed cognitive function parameters were compared to work productivity measures with 75 BCS and 75 women who have never been diagnosed with cancer. As shown in Figure 2, the parameters were completed online. All data analysis was performed on SPSS version 14 and 16 and the data was stored at the Uniformed Services University of the Health Sciences (USUHS). The participants completed a series of self-report measures of cognitive limitations, depressive symptoms, fatigue, and work limitations as well as a remotely administered neuropsychological probe. The self-reported measures included the Work Limitations Questionnaire (WLQ; Lerner et al., 2001), Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF; Stein et al., 2004), the Functional Assessment of Cancer Therapy-Cognitive scale version two (FACT-COG, Cella et al., 1993), and the Cognitive Symptoms Checklist-modified (CSC, Feuerstein et al., 2007; Hansen et al., 2008). The online neuropsychological probe was the CNS Vital Signs ® (Gualtieri & Johnson, 2006). Participants were randomized to study procedure 1) self-report measures followed by behavioral probe or two) behavioral probe followed by self-report measures. The procedures are summarized in Figure 2.

Breast Cancer Survivor Group. Seventy-five breast cancer participants were enrolled in the study. Inclusion criteria for this group consisted of adult female BCS, between the ages of 18 and 65, who are working full-time during the time of assessment. BCS were at least one year, but not more than ten years,

from completion of primary treatment (surgery, chemotherapy, radiation therapy, or a combination of treatments). BCS of all ethnicities were recruited. The participants had computer/Internet access and usage. Participants were required to have Internet speed higher than dial-up to proceed with study.

Non-Cancer Comparison Group. Seventy-five women were recruited for the NCCG. The comparison group consists of adult females of all ethnicities and of working age during the time of the assessment (18 through 65 years old) that have never been diagnosed with cancer. Participants had computer access and usage and will be working at time of assessment, at Internet speeds greater than the dial-up speed.

Exclusion criteria. Exclusion criteria for both groups include a diagnosis of dementia, brain injury, adult attention deficit hyperactivity disorder (ADHD), epilepsy, drug or alcohol abuse, or metastasis cancer.

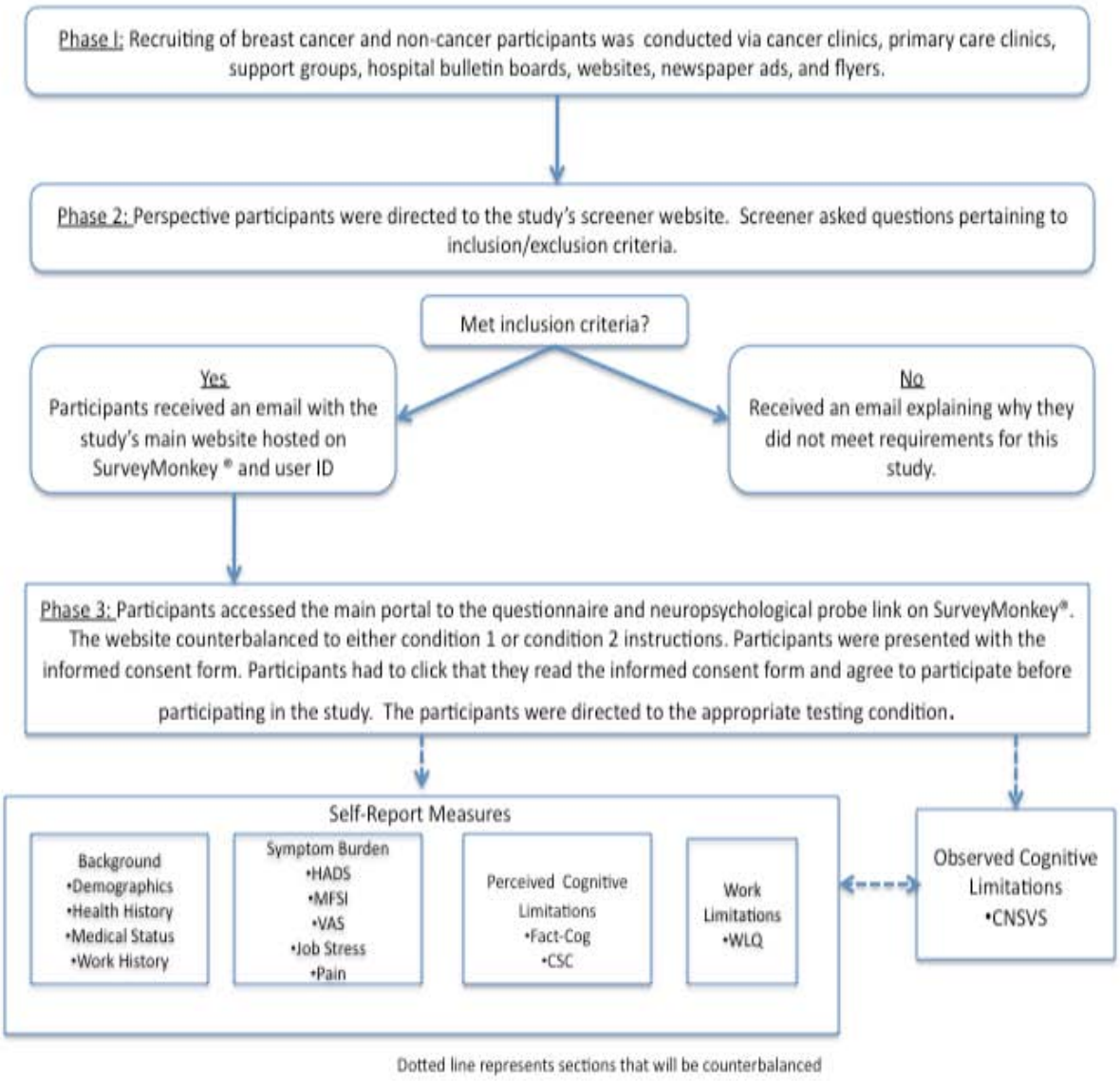
Procedures

BCS and controls were recruited by ads and flyers. Different ads and flyers were used to recruit both groups. Ads and flyers were placed at cancer clinics/centers and primary care clinics across the US, support groups, hospital bulletin boards, newspaper ads, and websites. All recruitment materials directed participants to a specific website that links to the screener website hosted by SurveyMonkey® to fill-out the screening information. Participants that met inclusion criteria were counterbalanced to a test condition (1-self-report followed by behavioral probe; 2-behavioral probe followed by self-report). They were sent an email with their identification number and study's main website, which acted

as a portal and was hosted by SurveyMonkey®. Upon logging into the main website, the participants were presented with the informed consent form. Participants were required to click that they have read and agree to participate with the study in order to proceed with the site. After agreeing to participate, the participant was guided to the main portal page, which provided instructions and links for the study. The self-report portion of the study and the behavioral probe were hosted on separate websites. The self-report measures were placed on a website hosted by SurveyMonkey®. The behavioral probe was conducted on the CNSVS® website, which was a secure, HIPAA compliant website hosted by CNS Vital Signs, LLC, based in Chapel Hill, NC (www.cnsvs.com). The study's main website linked directly to the CNSVS® and SurveyMonkey® websites. Individuals with identification numbers ending in an odd number received instructions for condition one (see appendix E). Individuals with identification numbers ending in an even number received instructions for condition two (see appendix E). During the self-report phase, all participants were asked to fill out information regarding their demographics, health history, work history, measures of emotional and physical health, job stress, perceived cognitive limitations, and work productivity. The order of self-report and neuropsychological probes was counterbalanced in order to account for fatigue and other confounding variables associated with order of measures. Furthermore, individuals were able to take a break in between the neuropsychological probe and the self-report portion. Identification number was used to match self-report and neuropsychological responses. The identification number consisted of a three digit random number from a random

number list. The random number list was created with an online random number list generator program (http://www.lextutor.ca/tools/rand/). See appendix B for the random number list. The participants were provided with a choice of either a cancer survivorship book or a stress reduction workbook upon completion of the study. Participants provided sensitive information (name, contact information, social security number) in order to receive the book. The data was stored electronically in a password protected computer in a locked laboratory at USUHS. At the end of the study, the participants were provided with a list of online resources and agencies that specialize in psycho-oncology and supportive services. Participants were asked if they would like to receive information regarding the overall results of the study at a later date. Participants who clicked yes to this question, will be sent an email at a later date describing the final results of the study.

Figure 2: Study Procedures



Dotted line represents sections that will be counterbalanced

Measures Obtained During the Study

Demographics, Medical, and Work Status. Participants completed questions regarding demographics, medical, and work status. Demographic questions included questions on ethnicity, race, age, marital status, and education. Medical questions included location of tumor, stage of tumor, treatment received (i.e., surgery, radiation, chemotherapy), time elapsed since completion of treatment, medications, menopausal status, and the presence of any pain via a pain visual analogue scale (Scott & Huskisson, 1979). Work related questions included type of occupation, average number of hours worked per week, job satisfaction, and number of sick days used in the past year.

Work Limitations Questionnaire (WLQ). The WLQ is a 25 item self-report measure of the impact of chronic health problems on productivity and work (Lerner et al., 2001). The higher a person scores on this measure, the lower their productivity (higher limitations) at work. This measure has been used on groups with diverse medical problems such as chronic headaches and epilepsy (Lerner et al., 2003). The WLQ is composed of subscales for time demands, physical demands, mental-interpersonal demands, and output demands. The time, mental-interpersonal, and output scale items referred to the amount of time that emotional or physical health problems have made it difficult to perform specific job demands (Lerner et al., 2001). The output demand scale had the highest internal consistency (Cronbach $\alpha = 0.9$) of all four scales. The output demand scale is considered to accurately predict productivity loss. As a result, the output demand scale will be the outcome of interest.

Measure of observed and perceived work limitations. There currently is no "gold standard" measure of work limitations or work productivity. However, when evaluating the self-reported measures of work productivity, the WLQ is comparable to other perceived and observed measures and is one of the more extensively reviewed and used measures (Mattke, Balakrishnan, Bergamo, & Newberry, 2007). The WLQ has been used in several medical populations (Lofland, Pizzi, & Frick, 2004), including working BCS (Hansen et al., 2008). Prasad and colleagues (2004) reviewed 12 measures of work productivity and concluded that the "Work Limitations Questionnaire is a valid self-report instrument, providing an accurate portrayal of the role of a worker's health in labor productivity" (Prasad et al., 2004, p. 233). The WLQ has been validated against performance-based measures of work limitations with 800 telephone operators and 120 warehouse personnel. These studies found that the WLQ was related to observed work limitations (Amick et al., 2000; Allen & Bunn, 2003; Lerner et al., 2003). As a result of its sound psychometric properties and its ability to measure performance-based measures of work limitations, the Work Limitations Questionnaire was selected as a measure of perceived and observed work limitations.

Hospital Anxiety and Depression Scale (HADS). The HADS (Zigmond & Snaith, 1983) is a self-assessment scale for measuring depressive symptoms and anxiety in a general medical population. The HADS consists of 14 items on two subscales, one measuring Anxiety (A-scale) and one measuring Depression (D-scale), which are scored separately. The HADS has been used to found to

adequately assess for depressive symptoms and anxiety in cancer patients (Hopwood, Howell, & Maguire, 1991) and has been used extensively to evaluate depressive symptoms and anxiety symptoms in the cancer population (Poppelreuter et al., 2004; Spiegel & Giese-Davis, 2003). The HADS has also been found to have high concurrent validity with the Beck Depression Inventory and State-Trait Anxiety Inventory (STAI) and to be effective in detecting anxiety and depressive symptoms in control (non-medical) samples as well as medical samples (Michopoulos et al., 2008). The HADS was included as a measure of perceived depressive and anxiety symptoms.

Single-Item Measures of Fatigue. A review of over 20 fatigue measurement tools indicated that cancer survivors were able to adequately assess their level of fatigue by using a single-item measure of fatigue (Jean-Pierre et al., 2007). An item measuring cancer-related fatigue has been extracted from the larger measure, the Rotterdam Symptom Checklist (de Haes, van Knippenberg, & Neijt, 1990). This single item has been used in the literature to assess for fatigue. The measure consists of three portions: tiredness, lack of energy, and difficulty sleeping (Jean-Pierre et al., 2007). The item from the Rotterdam Symptom Checklist, along with a visual analogue scale of fatigue will be used in order to assess presence and magnitude of general fatigue (Jean-Pierre et al., 2007).

Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). The MFSI-SF (Stein et al., 2004) is a 30-item self-report measure of fatigue encompassing five symptom domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor. Depressive symptoms can contribute to fatigue

and may impact perceived measurement of fatigue (Jean-Pierre et al., 2007). As a result, a multi-dimensional measure of fatigue was considered in addition to a single-item measure of fatigue. The MFSI allows for the measurement and separation of emotional and mental fatigue, which may be related to depressive symptoms. In an effort to control for redundancy of measurement (e.g., components of emotional and mental fatigue being captured by depression measure), the MFSI-SF subscale of physical fatigue was a dimension of interest.

Jean-Pierre et al. (2007) evaluated over 20 measures of fatigue and concluded that the MFSI is comparable to other multi-dimensional measures of fatigue. The MFSI has been validated with the breast cancer population and was able to detect differences in fatigue between healthy controls and breast cancer patients with and without anemia. The MFSI was able to detect differences in fatigue in breast cancer patients who received different cycles of anthracycline-based chemotherapy (Mills, Parker, Dimsdale, Sadler, & Ancoli-Israel, 2005). This measure is able to detect higher levels of fatigue in BCS, compared to controls, and was able to detect higher levels of fatigue in cancer survivors who had more intense adjuvant chemotherapy treatment (Jean-Pierre et al., 2007; Mills et al., 2005).

Job Stress (from the Behavioral Risk Factor Survey). One question will be extracted from the Behavioral Risk Factor Surveillance Survey (Centers for Disease Control and Prevention, 1999) to assess for frequency of high perceived job stress. This measure of perceived job stress asks the participant to rate how often (never, seldom, sometimes, or often) they think their current work situation

puts them under too much stress. This measure has been used previously in cancer survivors and work studies (Feuerstein et al., 2007; Hansen et al., 2008).

Substance use prior to the test. Another possible confounder may be substance use (e.g., caffeine, nicotine, alcohol) prior to taking the online questionnaire and neuropsychological test. Most studies have accessed the effects of these substances through objective measures (e.g., breathalyzer results, blood withdrawal, and urinalysis). However, due to the online administration of this study, we used subjective measures of substance use. Caffeine can raise alertness, reaction time, and improve concentration, and activity endurance; however, it may also increase symptoms of anxiety (Bell & McLellan, 2002; Peeling & Dawson, 2007). Caffeine has a more pronounced effect on alertness, reaction time, and other measures of brain activity with individuals who do not normally consume caffeine. The maximum effect of caffeine takes place, on average, one hour after ingestion (Peeling & Dawson, 2007). Questions from the caffeine consumption questionnaire (accessed online from http://www.drkeddy.com/client/caffeine.pdf) are commonly used to assess caffeine consumption. The Behavioral Risk Factor Surveillance System Questionnaire (accessed online from http://www.cdc.gov/brfss/questionnaires/pdf-ques/2007brfss.pdf) and the CDC website (accessed online from: http://www.cdc.gov/NCHS/data/nhanes/nhanes_01_02/sp_smq.pdf) contain several questions on nicotine and alcohol consumption. Nicotine and alcohol can impact results on neuropsychological tests in different ways, depending on dose

and time since consumption. Nicotine in regular users has been noted to increase concentration and alertness, while it suppresses cognitive function in individuals who do not regularly consume tobacco products (Newhouse, Potter, & Singh, 2004). Large amounts of alcohol serve to decrease cognitive function in both regular users and individuals who do not regularly consume alcohol. Also, gender differences must be taken into consideration, particularly when accessing for the effects of alcohol (Baraona et al., 2001). Alcohol persists longer in the female system than in the male body. For instance, it takes an average of 73 minutes for 50 percent of orally ingested alcohol (that makes it past first pass metabolism) to be gastrically cleared in women, while this process takes an average of 51 minutes in males. There are lingering and stronger effects of alcohol in women than in men, and this should be considered when assessing neurocognitive function in women (Baraona et al., 2001). As a result, time since consumption and amount of alcohol were taken into consideration when addressing substance use, particularly in our study sample that only includes women.

Functional Assessment of Cancer Therapy Cognitive Scale Version two (FACT-Cog). The FACT-Cog (Wagner, 2003) is a 50 question self-report measure designed to measure cognitive limitations in cancer survivors. The scale measures the frequency of either positive (e.g., mental acuity) or negative cognitive functioning (e.g., problems concentrating) over the most recent seven days on a five-point likert-type scale (ranging from 0 = never to 4 = several times a day). This measure gives several scales looking at different aspects of

cognitive function. The Perceived Cognitive Impairment (PCI) and Impact of Perceived Cognitive Impairments on Quality of Life (PCIQOL) were used in this study in order to assess perceived cognitive function and its impact on functioning and quality of life. For these measures, lower scores are indicative of poorer symptoms or functioning.

Jacobs and colleagues (2007) administered the FACT-Cog to 101 cancer survivors and reported that the FACT-Cog has an internal consistency range of $\alpha = 0.97$ (total score) to $\alpha = 0.58$ (concentration subscale). While the psychometric properties are currently being established, Jacobs et al. (2007) found that the FACT-Cog has similar psychometric properties as the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 Cognitive Functioning scale (EORTC-CF), which is a commonly used measure of attention and memory. Jacobs et al. (2007) found that the FACT-Cog gave information on a broader range of cognitive domains and provided a broader scope on the cancer cognitive experience.

Cognitive Symptom Checklist-modified (CSC). The Cognitive Symptoms Checklist (CSC) was developed for use as a patient checklist to assist in orienting providers to patient reported cognitive problems (O'Hara, Harrell, Bellingrath, & Lisicia, 1993). The CSC was modified to a self-report index of disruption of work tasks that require specific cognitive functions (dichotomous discrimination; i.e., problem/not a problem). The CSC has been used to assess patient reported cognitive limitations in individuals with neurological insults, such as head injuries and brain tumors. These problems include

attention/concentration, memory, visual processes, and executive function. In a previous study (Feuerstein et al., 2007), the items were reduced from 100 to 83 items following factor analysis (varimax rotation) that revealed a three-factor solution (working memory, executive functioning, and attention). The CSC was further reduced to 59 items by selecting only items with a factor loading of 0.4 or higher on one of these three factors: memory, attention, and executive functioning. This version of the CSC was used as a measure of perceived cognitive limitations encountered by participants in daily life and at work with regards to the domains of memory, attention, executive function, and overall cognitive function.

CNS Vital Signs (CNSVS). The CNSVS is a computerized neurocognitive battery that measures memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility. The battery is comprised of several well-established neuropsychological tests, such as finger tapping, symbol digit coding, the Stroop test, and the continuous performance test. The CNSVS takes about 30 minutes to complete in its entirety.

CNSVS reliability. The CNSVS subscales have strong correlations with traditional neuropsychological tests and good test-retest reliability (see Appendix H). CNSVS test-retest values for attention (r = 0.65), memory (r = 0.66), psychomotor speed (r = 0.88), cognitive flexibility (r = 0.71), and reaction time (r = 0.75) were good when compared to the traditional paper-pencil neuropsychological batteries and other computerized neurocognitive batteries (Gualtieri & Johnson, 2006). For example, for the domain of memory,

conventional tests in general have a test-retest of r=0.70; computerized neuropsychological tests in general have a r=0.60, Headminder (a computerized neuropsychological test) has a test-retest r=0.58, and the CNSVS has a test-retest r=0.65. CNSVS Shifting Attention Test correct scores (0.773), errors (0.697) and efficiency (0.694) correlated highly with traditional neuropsychological Shifting of Attention Tests. Hence, the CNSVS has psychometrics comparable to conventional and computerized neuropsychological tests (Gualtieri & Johnson, 2006).

The CNSVS test has been validated with a normative sample and has been used to detect mild and moderate cognitive limitations in numerous neuropsychiatric patients, such as patients with mild and severe brain injured patients, early dementia, post-concussion syndrome, attention deficit hyperactivity disorder (ADHD), and depression (Gualtieri & Johnson, 2008a; Gualtieri & Johnson, 2006). The screen was tailored to correspond with the domains of interest and corresponding subtests are: memory (verbal memory test and visual memory test), executive function/cognitive flexibility (shifting attention test), and attention (continuous performance test). Scores were given as subject score (raw score), standardized score, percentile, and in performance categories (above, average, low average, low, very low). See Table 1 for description of subtests. The CNSVS was used because of its sound psychometrics when compared to traditional neuropsychological tests and other computerized neurocognitive batteries, it's sensitivity to detect mild cognitive limitations in a variety of medical populations, and the test's ability to measure

the cognitive domains of interest (attention, memory, and executive function) in a brief screener.

Table 1: CNSVS Test Summary

Cognitive Domain	Subtest	Description
Memory	Verbal Memory Test (VBM)	Participants are asked to remember 15 words and recognize them in the presence of 15 distractor words. The task is done at the beginning (short delay) and towards the end (long delay) of the battery. The lower the score, the more verbal memory impairment is present.
	Visual Memory Test (VIM)	Participants are asked to remember 15 geometric shapes and recognize them in the presence of 15 distractor shapes. The task is given at the beginning (short delay) and towards the end (long delay) of the battery. The lower the score, the more visual impairment is present.
Attention	Continuous Performance Test (CPT)	This test measures sustained attention. Participants are required to attend to the stimulus "B". The target stimulus is randomly presented 40 times, and non-target stimuli are presented 160 times. Participants must respond to the designated stimuli when flashed on the screen. A long response time may suggest cognitive impairment. Errors (more than four) are indicative of attention problems.
Executive Function/ Attention	Shifting Attention Test (SAT)	The SAT measures executive control and cognitive flexibility. Individuals are tested on accuracy and speed when asked to shift instructions. In one task, participants are shown a main shape and two shapes at the bottom of the screen. They are asked to match shapes either by shape or color. The task shifts at random. Participants are to make as many correct matches as possible.

Source: CNSVS Assessment Scoring Report; retrieved from http: www.cnsvs.com

Statistical Analyses

Several analyses were conducted to investigate the hypotheses of the study. Differences in demographics between the groups were analyzed with Chi-Square analyses. In order to assess the relationships between job characteristics, symptom burden, neuropsychological probe and self-report measures, regression analyses, partial correlations and Multivariate Analysis of Covariates (MANCOVA) were conducted.

Hypothesis 1. Perceived cognitive limitations will contribute to work limitations to a greater degree than observed cognitive limitations in both groups accounting for demographic, medical history, occupational characteristics, and symptom burden (depressive and anxiety symptoms, fatigue).

Hypothesis 1a. There will be a stronger relationship between fatigue and work limitations in breast cancer while there will be a stronger relationship between depressive symptoms and work limitations in the NCCG (based on our previous work).

Data Reduction Technique. Multivariate regression analyses were conducted. Due to the large number of possible confounders and power

limitations, a data reduction technique was employed (Tabachnick & Fidell, 1996). This analysis was conducted in two parts. The first analysis consisted of a linear regression model included all of proposed confounders measured (e.g., age, education level, marital status, menopausal status, history of adjuvant cancer treatment, measures of fatigue, job stress, pain. depressive and anxiety symptoms, substance use prior to/during the test, distracters during the test, Internet speed). All measures that met the $p<0.10$ criteria from the first analysis were entered into the final regression model. The dependent variable for both the data reduction regression and the final regressions was the output demands scale of the WLQ.

Statistical Analysis. As described above, linear regressions were conducted separately for BCS and NCCG. For the final linear regressions, the first step consisted of confounders that were significant from the data reduction technique. The second step included the cognitive performance test measures. The third step included the perceived cognitive limitations measures.

After the data was collected, it was noted that 39.3 percent of the participants (50.7 percent of NCCG v. 28 percent of BCS) reported no work limitations (WLQ=0). This trend in the data highlighted the need to assess the factors were related to the presence/absence of work limitations. As a result, a logistic regression was added to the analysis. The continuous score for WLQ Output Demands scale was converted to a dichotomous variable (WLQ =0; WLQ > 0). The logistic regression would allow for the assessment of increased risk associated with each variable. However, with a logistic regression, the ability to

evaluate individual differences or variance is lost (Field, 2005). As a result, it was deemed appropriate and beneficial to conduct both a linear and logistic regression.

Hypothesis 2. BCS will endorse greater symptom burden (depressive and anxiety symptoms, fatigue, and cognitive limitations) than the NCCG.

Statistical Analysis. A MANCOVA was conducted to examine differences in emotional and physical symptoms (depressive symptoms, anxiety, fatigue, cognitive limitations) between groups while accounting for demographic differences in age, race, and marital status. Furthermore, the MANCOVA analysis also examined differences between self-report of cognitive limitations and performance tests between the two groups.

Hypothesis 3. The relationship between observed and perceived cognitive limitation measures will be significantly different.

Statistical Analysis. Partial correlations were conducted to examine the relationship between observed and perceived cognitive limitations, while controlling for demographic differences between the two groups. The partial correlations were conducted with both the BCS and the NCCG combined, and each group was also analyzed separately.

Power Analysis

Several power analyses were calculated. The first set of power analyses was based on means and standard deviations of the self-report measures used in this analysis found in the literature (Hansen et al., 2008; Osborne et al., 2004; Prue et al., 2006; Vardy, et al., 2006). The nQuery® software used to calculate

power. It was determined that 61 participants were needed per group, for a total of 122, to detect a difference at an effect size of 0.5, 80 percent power, for a two-sided test at a significance level of 0.05 (Cohen, 1988). In order to account for participant drop-outs and incomplete data, 150 participants were recruited (75 per group).

Results

Participant Demographics. Table 2 presents demographics of the participants (N=150). Chi-square analysis indicated that the two groups differed in age (p=0.000), race (p=0.01) and marital status (p=0.03). BCS tended to be older, less racially diverse, and more likely to be married/cohabitating than the non-cancer comparison group (NCCG). There were no significant differences in ethnicity (p=0.12) and education (p=0.80). Both groups indicated that they were highly educated (e.g., 87 percent of BCS and 90 percent of NCCG indicated having an associates degree or higher). With regard to menopausal status and breast cancer, 42.7 percent of BCS reported that they were premenopausal prior to cancer and remained so post-cancer; 46.7 percent of BCS reported becoming menopausal post-cancer; and 9.3 percent reported being menopausal prior to their cancer diagnosis. A significant portion of the BCS sample reported that they had become post-menopausal after cancer (p=0.000). At the time of their participation in this study, menopausal status did not differ between the BCS and NCCG (p=0.88) as 64 percent of BCS and 79 percent were pre-menopausal or beginning to transition into menopause.

Job Characteristics. Table 3 presents job characteristics for both groups (N=150). Chi-square analyses revealed no significant differences in years at job (p=0.23), annual income (p=0.70), and type of employment (p=0.48) between groups. The analysis of job characteristics of BCS pre- and post-cancer revealed no significant changes in job characteristics after cancer (p=0.07). BCS reported more job satisfaction than NCCG (p=0.02).

Treatment and Lost Days of Work for BCS. As indicated in Table 4, the BCS participants (n=75) averaged 2.9 years post-treatment. Over 50 percent of BCS group reported cancer in their right breast. Only one participant reported cancer in both breasts. The majority of the BCS were diagnosed during Stage II (44 percent), followed by Stage I (37.3 percent), Stage III (16 percent), and Stage 0 (2.7 percent). Note: Stage IV survivors were excluded from the study. All but one BCS participant was treated with surgery (98.7 percent). The majority of BCS participants were also treated with chemotherapy (81.3 percent) and radiation therapy (73.3 percent). Tamoxifen (44.0 percent), Herceptin (16 percent) and other treatments (24 percent) were used to a lesser extent. With regard to breast cancer and return-to-work, the majority of BCS (78.7 percent) reported returning-to-work within six months of treatment completion. Over one-third of the BCS (36 percent) reported no job absence after their cancer diagnosis.

Hypothesis 1 (Data Reduction Step). The linear regression was conducted in a two-step process, as described in the analysis section. Variables consisting of demographics, medical history, occupational characteristics, and symptom

burden (psychological and physical) were entered into the first regression. For the BCS group, physical fatigue (MFSI-SF score; β=0.36, p=0.01), depressive symptoms (HADS-D score; β=0.46, p=0.01), and having Stage III cancer (β=3.36, p=0.03) were significant confounders, and were consequently entered into the first step of the main regression for the BCS group. For the NCCG, depressive symptoms (HADS-D score; β=0.46, p=0.01) and generalized pain (VAS-P scale; β=0.45, p=0.06) were the proposed confounders who met the p<0.10 criteria, and as a result, these variables were entered into the first step of the main regression for NCCG.

Hypothesis 1 (BCS Linear Regression). Table 5 displays the results from the linear regression analyses for the BCS group (n=68) and NCCG (n=66). For the BCS group, proposed confounders accounted for 43 percent of the variance in work limitations (R^2=0.43, p=0.000), and self-report measures of cognitive function accounted for 19 percent of the variance in work limitations (R^2=0.19, p=0.000) after accounting for proposed confounders and performance tests. Performance tests did not significantly account for the variance in work limitations (R^2 Change=0.04, p=0.57) after accounting for proposed confounders. The overall model accounted for 66 percent of the variance in work limitations for the BCS group (R^2=0.66, p=0.000). Fatigue significantly accounted for variance in work limitations (β=0.23, p=0.04) in the BCS group.

Hypothesis 1 (NCCG Linear Regression). For the NCCG, proposed confounders accounted for 25 percent of the variance in work limitations (R^2=0.25, p=0.000) and self-report measures of cognitive performance

accounted for 28 percent of the variance of work limitations (R^2=0.28, p=0.000) after accounting for proposed confounders and performance tests. Performance tests did not significantly account for the variance in work limitations (R^2=0.10, p=0.14) after accounting for proposed confounders. The overall model accounted for 63 percent of the variance in work limitations for the NCCG (R^2=0.66, p=0.000). Depressive symptoms significantly accounted for work limitations in the NCCG (β=0.24, p=0.02). For both groups, self-report of cognitive limitations accounted for a larger percentage of variance in work limitations than performance testing. These results support hypothesis 1: perceived cognitive limitations will contribute to work limitations to a greater degree than observed cognitive limitations in both groups after accounting for proposed confounders.

Multicollinearity. It was noted that several factors within the performance testing step and within the self-report of cognitive limitations step were highly correlated and in possible violation of the linear regression assumption of the multicollinearity. (e.g., no linear linear relationship among predictors; Field, 2005). For example, within the performance testing for the NCCG, correlations indicated that the executive function and attention variables were highly correlated (r=0.96). In the regression for the NCCG, these highly correlated variables were significant even though the R^2 change for the entire group was not significant, which could be an indicator of multicollinearity. Multicollinearity does not affect the predictive power or reliability of the regression analysis; however, there are limits to the interpretations of the regression analysis (O'Brien, 2007; Schroeder, Lander & Levine-Silverman, 1990).

The performance tests for executive function and attention were highly correlated which indicates that the coefficients for the individual independent variables are not interpretable. Similarly, the subscales of self-reported cognitive limitations were highly correlated. For example, for the BCS group, CSC Executive Function was highly correlated with CSC Overall Score (r=0.90). See tables 9 through 11 for partial correlations. When the predictors are highly correlated, they tend to act as a combined or bundled score. As a result, looking at the R^2 change is more meaningful/robust and the more appropriate measure than looking at the individual predictors within the performance testing and self-report of cognitive limitations steps (O'Brien, 2007). In addition, the variance-inflation factor (VIF) can be calculated to determine the degree to which the regression model (R^2) is negatively affected by multicollinearity by the equation: $VIF = 1/(1-R^2)$. The tolerance and VIF calculations indicated the possibility of multicollinearity with the performance tests and self-report measures of cognitive limitations. However, the VIF calculations for the overall linear regression models (VIF = 2.94 for BCS; VIF=2.70 for NNCG) indicated that the regression models were not significantly degraded by multicollinearity and the overall models for both NCCG and BCS were interpretable (Schroeder, Lander & Levine-Silverman, 1990).

Hypothesis 1 (Logistic Regressions). Table 6 presents the results from the logistic regressions. The logistic regressions allow for the assessment of odds ratios, a measure of effect size or likelihood of an occurrence, and a 95% confidence interval, or measure of reliability of the odds ratio results. Odds ratio

of one indicate that the presence of work limitations are equal for both groups and odds ratio of less than one indicate that the presence of work limitations is less likely in that group. An odds ratio of more than one indicates that the presence of work limitations is more likely in that group. Most of the odds ratios in the logistic regression were close to one or less than one. Verbal memory, visual memory, and CSC overall had odds ratio greater than one in the BCS group; however, their 95% confidence intervals expanded across a wide range, indicating a less reliable result (Field, 2005).

Hypothesis 1 (Logistic Regression for BCS). For the BCS group, the overall model was significant (p=0.000). All three blocks significantly contributed to the total Chi-Square (Confounder Chi-Square=23.07, df=3, p=0.000; Observed Cognitive Limitations Chi-Square=12.07, df=5, p=0.03; Perceived Cognitive Limitations Chi-Square=16.49, df=6, p=0.01). For BCS, perceived cognitive limitations contributed to work limitations to a greater degree than observed cognitive limitations (Table 6). As a result, this regression supports hypothesis one.

Hypothesis 1 (Logistic Regression for NCCG). For the NCCG (n=66), the overall model was significant (p=0.000; Table 6). Only proposed confounders significantly contributed to the total Chi-Square (Confounder Chi-Square=10.12, df=2, p=0.000; Cognitive Performance Test Chi-Square=7.50, df=5, p=0.19; Self-report of Cognitive Limitations Chi-Square=10.18, df=6, p=0.12). As a result, this regression supports hypothesis one.

Hypothesis 1 (Linear and Logistic Regressions Combined). When combining the results of both the linear and logistic regression, it appears that confounders significantly contributed to the presence of work limitations (BCS Confounder Chi-Square=23.07, df=3, p=0.000; NCCG Confounder Chi-Square=10.12, df=2, p=0.000) and the variance in work limitation score (R^2 Change=0.43 for BCS, p=0.000; R^2 Change= 0.25 for NCCG, p=0.000). Self-report of cognitive limitations contributed to the presence of work limitations (BCS Self-report Chi-Square=16.49, df=6, p=0.01; NCCG Self-report Chi-Square=10.18, df=6, p=0.12) and variance (BCS Self-report R^2 Change=0.19; NCCG Self-Report R^2 Change =0.28) in work limitation score to a greater degree than observed cognitive limitations (R^2 Change=0.04 for BCS, p=0.57; R^2 Change= 0.10 for NCCG, p=0.14; BCS Performance Test Chi-Square=12.07, df=5, p=0.03; NCCG Performance Test Chi-Square=7.50, df=5, p=0.19). After considering the results from both the linear (Table 5) and logistical regressions (Table 6), hypothesis one was supported.

Missing Data. It was noted that 11 percent of the participants (eight BCS, nine NCCG) had missing data and were excluded from the regression analysis. Additional analyses were conducted to evaluate the demographics of the participants with missing data and identify the independent variables that had missing data. The excluded participants did not differ in age (p=0.29), race (p=0.55), ethnicity (p=0.22), and marital status (p=0.92) from the remainder of the sample. In addition, there were only three variables in the linear regressions that had missing data: Fact-Cog PCI (12 missing), Fact-Cog PCIQOL (three

missing), and Visual Analogue Scale for Pain (three missing). The Fact-Cog PCI had the most missing values and rendered further examination. The Fact-Cog PCI means did not differ between the excluded and included participants. When the Fact-Cog PCI was excluded from the regression analyses, no significant changes occurred in the overall results. For example, without the Fact-Cog PCI in the model, the overall R^2= 0.61 for BCS, compared to R^2= 0.66 when Fact-Cog PCI is included. In addition, the same trends were observed in R^2 change results when Fact-Cog PCI was excluded from the model. It was concluded that the missing data of the Fact-Cog PCI did not negatively impact Fact-Cog PCI contributions to the overall model. As a result, the Fact-Cog PCI was included in the final regressions.

Measures of Substance Use. Additional regressions were conducted to determine if measures of caffeine (BCS p=0.93; NCCG p=0.95), alcohol (BCS p=0.81; NCCG p=0.97) or nicotine usage (BCS p=0.77; NCCG p=0.40) significantly contributed to the variance in the cognitive performance tests. The results indicated that these measures of substance use did not significantly contribute to observed cognitive performance scores.

Hypothesis 1a. Both the linear regressions and logistic regressions indicated that the proposed confounders significantly accounted for variance in work limitations and contributed more to the total Chi-Square when each group is evaluated separately. When the groups were evaluated separately, physical fatigue significantly accounted for the variance for the BCS group (β=0.23, p=0.04), and depressive symptoms significantly accounted for the variance for

the NCCG (β=0.24, p=0.02). However, it would be important to analyze if these interactions would be present if the groups were evaluated together. Hence, a multivariate linear regression was conducted where both groups were combined and interactions for depressive symptoms by cancer group and physical fatigue by cancer group were evaluated. This analysis was conducted to test for hypothesis 1a: there will be a stronger relationship between fatigue and work limitations in BCS while there will be a stronger relationship between depressive symptoms and work limitations in the NCCG.

Table 7 presents the results of the linear regression evaluating for these interactions (N=133). The first step contained cancer status and three of the confounders that applied to both groups from the previous regressions. Stage III cancer was not used because it did not apply to NCCG. The interactions of interest (fatigue x cancer status, depressive symptoms x cancer status) were placed in the last step. As in previous regressions, confounding variables (R^2=0.34, p=0.000) significantly accounted for the variance in work limitations score. After accounting for the contributions of proposed confounders, cognitive performance testing did not significantly account for the variance in work limitations (R^2= 0.04, p=0.18). After accounting for the contributions of proposed confounders and cognitive performance tests, self-report of cognitive limitations (R^2=0.26, p=0.000) significantly accounted for the variance in work limitations score. After accounting for the contributions of proposed confounders, cognitive performance tests, and self-report of cognitive limitations, interaction variables for cancer status by depressive symptoms and cancer status by fatigue were not

significant (R^2=0.01, p=0.18). Table 7, Figures 6 and 7 illustrate that the interactions are in the predicted direction; however, the interactions are either on the edge of the data and slightly crossing (Figure 7), or not crossing at all (Figure 6); hence, not statistically significant. This analysis does not support Hypothesis 1a.

Hypothesis 2. A MANCOVA was performed (N=132) to investigate hypothesis two, where age, marital status and race were the covariates (Table 8). The results indicate that when differences in age, marital status and race are accounted for, the BCS group significantly reported more depressive symptoms (p=0.000), physical fatigue (p=0.000), and general fatigue (p=0.000; Figure 4). BCS also reported more perceived problems with memory (p=0.000), executive functioning (p=0.000), overall cognitive functioning (p=0.000), more difficulties on the perceived cognitive impairment scale (p=0.000), and perceived cognitive impairment that affected quality of life scale (p=0.000; Figure 4). Anxiety (p=0.10) and self-reported attention (p=0.08) did not significantly differ between groups. Performance cognitive tests for composite memory (p=0.21), verbal memory (p=0.21), visual memory (p=0.41), executive function (p=0.18), and attention (p=0.36) did not significantly differ between the BCS and NCCG (Figure 5). The BCS group scored significantly higher than NCCG on the HADS-D (p=0.000), although both averages were within the normal range. The BCS group significantly reported more overall difficulties in several measures of symptom burden, supporting hypothesis two.

As part of the analysis of symptom burden, it was of interest to investigate whether the BCS group had performance-based cognitive limitations using an acceptable operationally definition of cognitive limitations. The International Cognition and Cancer Task Force recommended that future cancer studies use a systematic operational definition of cognitive limitations, such as one standard deviation below the mean of a reference group on performance tasks (Vardy et al., 2007). Hence, an additional analysis was conducted to investigate the number of BCS that would fit this operational definition of cognitive limitations using the CNSVS. Using this definition to analyze the CNSVS results, 9.33 percent of BCS experienced composite memory problems; 6.67 percent of BCS experienced deficits in verbal memory; 16 percent of BCS experienced deficits in visual memory; 2.67 percent of BCS experienced deficits in executive function tasks; and 5.33 percent of BCS experienced problems with an attention task. These rates of observed cognitive limitations are lower than what has been reported in previous studies, which report up to 35 percent of BCS experience observed cognitive limitations (Wefel, Witgert, & Meyer, 2008).

Hypothesis 3. Partial correlations (controlling for age, marital status and race) were conducted. Table 9 shows the partial correlations using all participants (N=135). Table 10 displays partial correlations for BCS only (n=68). And Table 11 presents partial correlations for NCCG only (n=68). All three tables show that after accounting for demographic differences, self-report tests were highly correlated with other self-report tests and performance tests were highly correlated with other performance tests. For example, when both groups were

evaluated together (Table 9), the performance test for composite memory was highly correlated (r=0.87, p=0.000) with the performance tests for verbal and visual memory. However, the performance test of composite memory had a very small correlation with self-report of overall cognitive function (r=0.04, p=0.69), memory (r=0.07, p=0.43), attention (r=0.01, p=0.91), executive function (r=0.00, p=0.99), Fact-Cog PCI (-0.12, p=0.19), and Fact-COG PCI QOL (r=-0.07, p=0.43). In general, WLQ score was significantly correlated with self-report measures of cognitive limitations, but was not significantly correlated with performance tests. For example, when both groups were evaluated together (Table 9), the performance test for composite memory had a small correlation (r=0.05, p=0.61) with WLQ output score, while the self-report measure of overall cognitive function had a large correlation (r=0.65, p=0.000) with WLQ output score. WLQ output score was significantly correlated (defined as $p<0.05$) with more self-reported measures of cognitive limitations with the BCS group (six measures) than the NCCG (four measures). These results support hypothesis three, in that the relationship between observed and perceived cognitive limitation measures were significantly different, and this trend appeared to be more prominent with the BCS group than with NCCG.

Explanatory Analysis. The results of the regressions and MANCOVA revealed that the BCS group and NCCG differed in factors contributing to the presence of work limitations, and in levels of perceived cognitive limitations, but not in cognitive performance test scores. As a result, regression analyses investigating the contributions of proposed confounders on cognitive measures

were warranted. Table 12 displays the results of eight regressions where either self-reported cognitive measures or performance measures were the dependent variables. For BCS (n=68), physical fatigue (β=-0.41, p=0.000) and depressive symptoms (β=-0.30, p=0.000) significantly contributed to Fact-Cog PCI. Physical fatigue (β=-0.46, p=0.000) and depressive symptoms (β=-0.36, p=0.000) significantly contributed to Fact-Cog PCI QOL (n=71). However, physical fatigue (β=-0.08, p=0.54) and depressive symptoms (β=-0.07, p=0.56) did not significantly contribute to performance test of attention (n=73). In addition, physical fatigue (β=-0.10, p=0.71) and depressive symptoms (β=0.05, p=0.71) did not significantly contribute to performance test of executive function (n=73). For NCCG, general pain (β=-0.28, p=0.02) significantly contributed to Fact-Cog PCI (n=66). General pain (β=-0.36, p=0.000) significantly contributed to Fact-Cog PCI QOL (n=72). However, general pain (β=0.18, p=0.14) and depressive symptoms (β=0.10, p=0.43) did not significantly contribute to the performance test of attention (n=73). General pain (β=0.17, p=0.17) and depressive symptoms (β=-0.06, p=0.64) did not significantly contribute to the executive function performance test (n=73). Furthermore, proposed confounders contributed more to self-reported measures of cognitive limitations in BCS than NCCG (36 v. 12 percent on the Fact-Cog PCI; 46 v. 18 percent on the Fact-Cog PCI QOL). Proposed confounders did not significantly contribute to the performance test scales, and this held true for both groups.

Perceived and Observed Cognitive Measures: Association to Work Limitations. Additional analyses were conducted based on the Vardy et al.

(2008) recommendations of standardizing the definition of cognitive limitations or deficits as one standard deviation below the mean of a reference group. These values were calculated for the BCS groups for both the perceived and observed measures of cognitive limitations. Work limitations were characterized as either no work limitations (WLQ=0) or presence of work limitations (WLQ>0). For the BCS, the presence of perceived cognitive limitations verses the presence of work limitations was compared in a Chi Square analysis. Also for the BCS, the presence of observed cognitive limitations verses the presence of work limitations was compared in a Chi Square Analysis. Table 13 displays the results of these analyses. A significant number of BCS who reported the presence of cognitive limitations also reported the presence of work limitations (For CSC Memory; Fact-Cog PCI, Fact-Cog PCI QOL p=0.000; For CSC Executive Function p=0.005; For CSC Attention p=0.005). However, women who had observed cognitive limitations did not significantly report work limitations (For CNSVS Composite Memory p=0.396; CNSVS Verbal Memory p=0.680; CNSVS Visual Memory p=0.250; CNSVS Executive Function p=0.482; CNSVS Attention p=0.314)

Discussion

Overall Findings

The overall results of this study indicated that BCS had higher overall symptom burden even three years post-diagnosis. The two groups differed in self-report of cognitive limitations but did not differ in their performance test results. When both groups were evaluated together, depressive symptoms, pain,

and physical fatigue significantly and independently accounted for the variance in work limitations regardless of cancer status. Self-report of work limitations had a stronger relationship with self-reported cognitive limitations than with cognitive performance measures. Looking at the data further, self-report of depressive symptoms, pain and fatigue influenced self-reported measures of cognitive limitations, and this relationship was more pronounced in BCS. However, self-report of depressive symptoms, pain and fatigue did not influence cognitive performance measures. These findings are consistent with studies and reviews (Shilling & Jenkins, 2007; Vardy et al., 2008) that indicated that depressive symptoms, distress, fatigue and other symptom burden measures were not associated with performance based cognitive tests, but were related to self-reported cognitive function.

Work Characteristics. The BCS participants indicated high rates of return-to-work soon after diagnosis. Approximately 90 percent of the BCS group was at work less than one-year post-diagnosis. This is consistent with other studies that have found between 79-88 percent of BCS continued to work six-months to one-year post diagnosis (Bouknight, et al., 2006; Bradley & Bednarek, 2002; Maunsell, et al., 2004) . In addition, BCS did not significantly change type of employment from time of diagnosis to almost three years post-diagnosis. Similar to the Maunsell et al., (2004) study, job characteristics of BCS were similar to that of NCCG of similar educational backgrounds.

Work Limitations & Job Satisfaction. BCS had more work limitations than the NCCG. BCS scored significantly higher on the work limitations measure and

had fewer incidences of absence of work limitations (WLQ = 0). For BCS, 28 percent reported absence of work limitations. For NCCG, 50.7 percent reported absence of work limitations. Despite having more work limitations, BCS reported significantly more job satisfaction than the NCCG. However, job satisfaction did not significantly contribute to work limitations in either group. This indicates that factors other than job satisfaction account for the variance in work limitations.

Symptom Burden. BCS reported higher levels of depressive symptoms, physical fatigue, general fatigue, and self-reported cognitive limitations almost three years post-diagnosis after accounting for demographic differences between the two groups. These findings are consistent with previous studies indicating that BCS, particularly those treated with chemotherapy, have more symptom burden, distress, and score lower on different measures of quality of life and these effects are experienced years post-diagnosis and treatment (Mehnert & Koch, 2008; Montazeri, 2008; Lee et al., 2007; Arndt et al., 2006; Ahles et al., 2005).

Although depressive symptoms were an independent and significant contributor to both cognitive limitations and work limitations, both the BCS and NCCG group scored within subclinical range on the depression measure. Hence, subclinical levels of depression can have significant implications on cognitive and work functioning for both BCS and NCCG. This is consistent with earlier work (Martin et al., 1996) that showed subclinical depression negatively impacted fulfillment of work roles (e.g., social and technical performance) in a community sample.

When both groups were evaluated together, factors that influenced work limitations were similar between groups (e.g., pain, fatigue, and depressive symptoms). Clinical implications of these results suggest that similar interventions can be employed with both BCS and NCCG in order to improve factors that impact work limitations. Several interventions have been developed to ameliorate the symptom burden of depressive symptoms, pain and fatigue (NCCN, 2009; Alfano et al., 2007; Biegler, Chaoul, & Cohen, 2008; Carson et al., 2007; de Maat et al., 2007; Ferguson et al., 2007; Ganz & Bower, 2007; Helgeson, et al., 2001; Markowitz, 2008; Mock, 2001; Nathan & Gorman, 2002; Savard et al., 2006). This research is discussed in more detail under the Clinical Implications and Future Directions subheading.

Operationally Defined Cognitive Limitations. Using Vardy et al. (2007) definition of cognitive limitations of one standard deviation below the mean of a reference group (in this case the NCCG), 2.67 to 16 percent of this BCS sample experienced cognitive deficits in a variety of observed cognitive domains (see Table 13). In addition, this BCS group did not significantly differ from the NCCG in the cognitive performance test. Studies have found cognitive differences between BCS and controls in neurocognitive performance tests and most studies have found observable cognitive limitations in 11 to 50 percent (averaging around one-third) of BCS (Ahles & Saykin, 2007; Ahles & Saykin, 2002; Anderson-Hanley et al., 2003; Schagen et al., 2001; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Vardy et al., 2008; Wefel, Witgert, & Meyers, 2008). However, when the same operational definition is applied to measures of

perceived cognitive limitations, 32 to 72 percent of this BCS sample experienced perceived cognitive limitations. Hence, BCS reported significantly more perceived cognitive limitations; however, their cognitive performance tests showed less cognitive limitations than other studies.

Possible Reasons for Discrepancy in Cognitive Limitation Measures. Several factors could help explain why the BCS group reported significantly more perceived cognitive limitations but scored similarly to NCCG on cognitive performance measures. These factors include sensitivity of the cognitive performance measures, abnormal illness behaviors, heightened sensitivity to change after breast cancer, demographics of BCS/high pre-morbid cognitive functioning in BCS, and biological factors related to being occupationally active.

Sensitivity of Measures. Although the CNS Vital Signs neurocognitive screen has been reported to detect mild and moderate cognitive impairment in a variety of populations, such as schizophrenics, mood disorder patients, and mild traumatic brain injuries (Gualtieri & Johnson, 2008a; Gualtieri & Johnson, 2008b; Gualatieri & Johnson, 2008), the CNS Vital Signs may not be the most sensitive screen to detect cognitive limitations in BCS. Meyers and Brown (2006) developed a paper-pencil brief neurocognitive battery to detect cognitive limitations for brain tumor survivors. However, more studies are needed to determine if this battery is the most sensitive for other groups of cancer survivors. The International Cognition and Cancer Task Force reported that currently there is no gold-standard for neuropsychological tests either in the paper-pencil or computer modality for BCS and more studies are needed to determine which

tests are most sensitive for this population (Vardy et al., 2008; Vardy, Rourke, & Tannock, 2007).

Computer Familiarity. Another possible explanation for the discrepancy may be due to the study's usage of a computer based cognitive screen instead of a paper-pencil neuropsychological battery. A recent study has found that degree of familiarity with computer use had a significant impact on several CNSVS subtests entailing rapid visual scanning and specific keyboard operations (e.g., Shifting Attention Test, Continuous Performance Tests), which would have affected the attention and executive function scores (Iverson et al., 2008). Hence, individuals who were very familiar with computers may have scored better on some of the performance measures than individuals who were less familiar with computers purely because they were more accustomed to working with computers. However, this sample was highly educated, working in highly technical or managerial positions, and was heavily recruited through a variety of modalities, to include different websites. As a result, it may be inferred that this sample of NCCG and BCS had high familiarity with computers and this phenomena may not have affected these results. Computer familiarity was not measured in this study so it is unknown if this phenomena may have contributed to the results indicating that the BCS and NCCG did not differ in performance tests.

Abnormal Illness Behavior. If the neuropsychological data were accurate, it may be the case that increased perceived cognitive limitations may be a result of an abnormal illness behavior. Juth, Smyth, and Santuzzi (2008) found that

negative self-esteem led to more negative affect, greater stress reactions, and greater self-reported symptom severity in chronically ill patients. Hence, it may be that while enduring cancer, a subset of women with low self-esteem identify as being sick or ill and subsequently develop abnormal illness behavior, such as having more stress reactions, over-reporting the severity of their symptoms, negative affect and functioning as a result of their illness. If this were the case, it could help explain why BCS were more likely to report more problems with their functioning. However, abnormal illness behavior has not been well studied in BCS, and its occurrence in high frequency may be an unlikely phenomenon.

Heightened Sensitivity to Change. Although medical technology and early screening procedures have increased the breast cancer survival rates, breast cancer diagnosis and treatment can be significantly distressing (Hegel et al., 2006). Hegel and colleagues (2006) reported that 41% of BCS experience clinically significant distress and meet criteria for a psychiatric diagnosis (e.g., major depression and post-traumatic stress disorder) when evaluated after diagnosis but before treatment of breast cancer. Hyper awareness and re-experiencing of a traumatic event (e.g., in the form of intrusive thoughts) are common symptoms of post-traumatic stress disorder. Mehnert, Berg, Henrich, & Herschbach (2009) reported that fear of recurrence did not decrease with more time since diagnosis and almost a quarter of BCS interviewed had moderate to high fear of disease recurrence or disease progression. It may be the case that for many BCS, the cancer experience was traumatic (Hegel et al., 2006; Mehnert et al., 2009) and as a result, BCS develop a heightened sensitivity to changes in

their body and functioning, such as cognitive functioning. A heightened sensitivity to changes in their functioning in BCS regardless of time since diagnosis and treatment would explain significantly higher perceived cognitive limitations in BCS. It could be the case, that hyper-aware BCS would be able to detect even small changes in their cognitive and work abilities.

Demographics as Potential Protective Factors. The demographics of this sample are indicative of a high pre-cancer cognitive function. In addition, several demographic factors of this BCS sample may help improve functioning. This sample of BCS was more likely to be married and have a high personally earned income, which Lavigne and colleagues (2008) found to be important protective factors against work productivity, and may be related to other functionality, such as cognitive function.

High Pre-Morbid Function. Another factor that might contribute to this discrepancy is that this BCS sample consists of highly educated women (i.e., 50 percent of BCS group had some graduate training or graduate degree) who were of high socioeconomic status (i.e., 84 percent were in managerial/administrative or technical/science occupations and 62.7 percent of survivors earned more than $100,000). It may be the case that these survivors had very high pre-morbid cognitive abilities that may have decremented after cancer, but were still within normal limits by neuropsychological standards. While still performing within normal limits on cognitive performance tests, this group of high functioning survivors may be highly aware of cognitive change. Even if the decline were subtle and cognitive performance were within the normal range by performance

test standards, the change in cognitive functioning appears to be very apparent to BCS and this subjective awareness in cognitive changes may be impacting work productivity.

Possible Biological Factors Related to Work & Cognitive Function. Breast cancer and treatment may impact brain structure and functioning. Silverman et al., (2007) found that BCS, even 5 to 10 years after treatment have alterations in their brain activity (e.g., cerebral blood flow pathways during neurocognitive exercises) as measured by positron emission tomography (PET) scans. The Silverman et al. (2007) study found that BCS cerebral blood flow pathways were more altered in BCS who received chemotherapy and tamoxifen combination treatment. The areas most affected were the basal ganglia, cerebellum, and frontal cortex, areas that impact motor coordination, voluntary movement, short-term memory and executive functioning or higher order coordination. While neuroscience and neuro-imaging studies are indicating that breast cancer and its treatment may have long term consequences to the brain structure and functioning, animal research has indicated that environmental enrichment can have positive effects on brain functioning. A study by Pereira and colleagues (2009) showed that environmental stimulation can increase brain oxidative activities to areas like the hippocampus and frontal cortex after brain damage (e.g., hypoxia-ischemia). Herring and colleagues (2009) found that environmental enrichment led to improved cellular plasticity in the hippocampus, impacted learning and memory in rats predisposed for Alzheimer's Disease related cognitive deficits.

Occupational environments could be considered as providing environmental enrichment in that it can serve as a source of social support and social stimulation, as well as a source of cognitive stimulation to an individual (Maunsell et al., 2004). Rat studies have shown that social stimulation and engaging in different activities and learning tasks can enhance neuroplasticity and cognitive performance (Elliott & Grunberg, 2005). Applying animal research findings to this context, it may be that BCS who are occupationally active may have enhanced recovery through neuroplasticity due to environmental, cognitive and social stimulation provided by the work place. Hence, it may be the case that after years of rebuilding neuropathways and improving regeneration in the hippocampus due to work-related environmental enrichment, occupationally active BCS may perform better on neuropsychological tests. The BCS in this study were working fulltime at the time of this study, were likely to work in cognitive challenging occupations (e.g., science, technology, administration), were on average 3 years post-diagnosis, and were working on average 7 years, with 90 percent returning to work within a year of cancer diagnosis and treatment. It may be the case that this sample performed better than other cohorts of BCS (e.g., non-occupationally active) because they benefited from the effects of environmental enrichment occurring in the workplace.

Clinical Assessments. The results of this study elucidate the importance of using self-reported measures of function (e.g., cognitive, work) in clinical assessments. Although someone may be performing “within normal limits”, she may be experiencing cognitive limitations or declines that are impacting other

areas in their life, such as work performance. The “gold standard” of neuropsychological tests may not capture or generalize to functional difficulties. Similarly, when assessing work limitations, it is important to measure perceived cognitive functioning and symptom burden (e.g., depressive symptoms, fatigue, pain).

Treatment of Symptom Burden. The explanatory analysis indicated that self-reported cognitive limitations were impacted by physical fatigue, and depressive symptoms; however, these factors did not significantly account for variance in performance tests. Hence, these results suggest that when mood, fatigue, or pain decrease, self-report of cognitive limitations may improve. Regarding performance tests, it could be that other independent factors that were not captured in this study may impact performance tests (e.g., cardiovascular fitness, sleep behaviors, specific chemotherapy regimens, etc.) More research is needed to determine factors that influence performance tests.

Potential Limitations

Cross-sectional. This study had potential limitations that could influence results. A cross-sectional study was appropriate given the nature of the research question investigated in this study (Vardy et al., 2008). However, there are limitations to our interpretations related to the cross-sectional nature of this study. For instance, causal relationship between cognitive limitations and work limitations, symptom trends, or work productivity over time cannot be assessed with the current data. Given the results of this study, it would be beneficial to measure BCS cognitive functioning prior to cancer treatment. This would enable

the assessment of the presence, magnitude, and disparity between perceived and observed cognitive decline throughout the cancer survivor trajectory. As a result, replication of this study in a longitudinal format with a measure of pre-morbid functioning is warranted.

Sample Bias. BCS were primarily recruited throughout the United States using flyers and websites. In addition, this study was administered through the Internet. Web-based recruiting and administration may limit generalizability, as not all BCS have access or use the Internet for breast cancer activities. While earlier studies indicated that BCS who accessed the Internet for cancer related topics were significantly younger and better educated than BCS who did not access the Internet (Pereira, et al., 2000), recent data suggested that over 75 percent of cancer survivors of various demographics and their families access the Internet for health information (Simon & Schramm, 2008). Furthermore, research indicated that a demographically diverse group of individuals were increasingly seeking medical information on the web, and Internet based studies of a large size actually recruit more demographically diverse samples (Whitehead, 2007). As a result, the literature indicated that selection bias of Internet studies may not be as great as it was originally thought to be (Whitehead, 2007), although it still may be present.

To combat the possible effects of selection bias and to recruit demographically diverse participants, this study was advertised in areas and hospitals that were ethnically and socioeconomically diverse. The study investigators connected with a wide variety of community members and

distributed study advertisements at nationally sponsored events that had a wide demographic of participants and community specific events that were targeted towards ethnically diverse populations. The investigators sought advertisements in websites that also catered to ethnically diverse cancer survivors, as well as websites that targeted the general population. Although there were individuals of different racial and ethnic origins represented in our sample, the participants were mostly Caucasian, highly educated and of high socioeconomic status. This may be due to our sample being a sample of convenience. These factors limit the generalizability of our results. Although efforts were in place to mitigate the possible effects of participant bias due to the nature of an Internet based study, it became apparent that more efforts were needed. For example, future studies may consider establishing computer stations within various communities to better account for access in low-income settings.

Bias due to Exclusion of Stage IV BCS. The scope of the study was limited to studying occupationally active breast cancer survivors, diagnosed with stage 0-III breast cancer. The majority of BCS research in the realm of work and cognitive limitations has been done in early stage breast cancer (stage 0-III). Furthermore, research that has investigated return to work in all stages of breast cancer has reported that women diagnosed with stage IV breast cancer are significantly less likely to return to work 12 months post-diagnosis and treatment (Bouknight, Bradley, & Luo, 2006; Johnsson et al., 2007). Due to the small proportion of stage IV BCS who return to work, this study focused on the majority of BCS who return to work (stage 0-III). While limiting the scope of the study

allowed us to get a better understanding of factors that influence the majority of BCS who return to work, limiting our scope also added to the possibility of sample bias. We cannot generalize the findings of this study to stage IV BCS. Future studies should address factors that impact work limitations in advanced staged BCS. Also, this study was focused on BCS who returned to work. More research should also aim to investigate differences in BCS who return to work and women who do not. Also, studies should focus on investigating factors that contribute to women who remain at work after returning to work, as well as women who decide to leave work after returning to work.

Environmental Factors. In order to recruit a diverse sample of BCS and NCCG across the United States, participants completed the online study using personal or public computers in their location of preference. While this allowed us to cast a wider net, this also added variability to the results due to different environmental factors (e.g., locations, use of different computers). Future studies should consider replicating this study in a laboratory or well-controlled environment in order to reduce the variance due to extraneous/environmental factors.

Participant Misrepresentation. Another potential confounder to the integrity of this study is the possibility of participant misrepresentation or inaccuracy of reporting information. As discussed in the Ethics and Internet-based Research section, several steps were put in place in order to decrease the risk of participant misrepresentation regarding their cancer status. A review of the data indicated that our BCS participants answered their cancer specific questions in a

way that was consistent with a breast cancer diagnosis and there was no indication of misrepresentation. Although we did not verify cancer status with medical records or their individual physicians, research indicates that BCS accurately report their medical history, to include cancer treatment, three-years post-diagnosis (Maunsell et al., 2005). As a result, there is little evidence that misrepresentation and inaccuracies in medical status reporting might have occurred in our study.

Measurement in BCS. Conventional neuropsychological evaluation is considered the “gold standard” for assessing cognitive function (Tannock, et al., 2004). The CNSVS is based on conventional neuropsychological tests and the CNSVS affords many benefits, such as ease of administration and scoring of a wide range of cognitive performance domains. The CNSVS has been shown to have strong correlations with standard neuropsychological batteries (correlations ranging between 0.65-0.88). While the CNSVS has been shown to be a reliable tool and is strongly correlated to standard testing (Gualtieri & Johnson, 2006) and has been found to detect mild cognitive changes in several reference groups, such as the mild traumatic brain injured (Gualtieri & Johnson, 2008), this neurocognitive screen may not be the most sensitive to determine mild cognitive limitations in BCS. In addition, Iverson and colleagues (2008) have recently published that frequency and familiarity with computer use impacts performance on several CNSVS subtests that involve rapid visual scanning and keyboard work. As a result, this study should be replicated using standard neuropsychological batteries in addition to a computerized neurocognitive

screen, while accounting for familiarity/frequency of computer usage. Although neuropsychological batteries are the “gold standard” of cognitive performance measurement, studies have used a wide variety of neuropsychological tests and the most sensitive measure of mild cognitive limitations for BCS is underdetermined (Vardy et al., 2008). It is unknown if the CNSVS or any other computerized neurocognitive screen is the most sensitive cognitive performance measure for BCS. Future studies should investigate which performance measures (computerized and paper-pencil format) are most sensitive to BCS groups (Vardy et al., 2008; Vardy, Rourke, & Tannock, 2007).

Multicollinearity. As mentioned in the results section, the perceived and observed measures of cognitive function measures were highly correlated. As a result, there were limits to the interpretation of the linear regression (e.g., interpret the R^2 change of the steps instead of the individual coefficients within each step). Future studies should seek to identify the best measures of observed and perceived cognitive limitations. Furthermore, index scores of overall cognitive function may also be appropriate when evaluating cognitive limitations in BCS (Vardy et al., 2008). Hence, future studies should replicate this study with the most sensitive measure of observed and perceived cognitive limitations for this population, and index scores of overall cognitive function should be included in the analysis. Identifying the most sensitive tool and using one overall score may decrease the possibility of multicollinearity in regression models and would increase the power of the analysis.

Absence of Work Limitations. A significant portion (39.3 percent) of the participants reported not experiencing any work limitations. This trend was significantly more in NCCG (50.7 percent) than BCS (28 percent). This information was consistent with prior research indicating that cancer survivors report more problems at work than individuals who have never been diagnosed with cancer (Bradley, Oberst, & Schenk, 2006; Feuerstein et al., 2007; Hansen et al., 2008; Hofman et al., 2007; Spelten et al., 2003). However, having a significant number of participants endorsing an absence of work limitations contributed to the variance in the data. A logistic regression was conducted in addition to the linear regression in order statistically reduce the chance of misinterpreting the data. It may be beneficial for future studies to screen for the presence of work limitations in order to reduce the variance and increase the likelihood of collecting normally distributed data with regards to work limitations. By only allowing individuals who were experiencing work limitations, it may decrease variance and make the findings more robust.

Clinical Implications and Future Directions

Assessments and Interventions. The results of this study show that after controlling for age, race, and marital status, BCS reported more symptom burden than women who have never been diagnosed with cancer. Although present and in the direction expected, interactions between depressive symptoms and cancer status, and fatigue and cancer status were not statistically significant. In addition, the main effects of pain, depressive symptoms and fatigue were significant when both groups were evaluated together. For this sample, it appears that breast

cancer treatment and breast cancer itself, did not significantly contribute to work limitations. These results suggest that pain, depressive symptoms, and fatigue contribute to work limitations for both groups; therefore, this implies that similar interventions could be used for both BCS and women without a history of cancer to improve work limitations.

Fatigue Interventions. Interventions for fatigue include exercise interventions and psychosocial interventions (e.g., educational group interventions and coping skills training; NCCN, 2009). Greater levels of physical activity (e.g., sports/recreational physical activities) have been associated with less fatigue and bodily pain at 39 months after breast cancer diagnosis (Alfano et al., 2007). A variety of aerobic exercise interventions have had positive results with breast cancer patients and BCS (Ganz & Bower, 2007). Studies using complimentary and alternative treatments, such as yoga, meditation, and acupuncture have reported evidence that these interventions were associated with lower pain (e.g., Aromatase Inhibitor related pain) and fatigue in BCS (Biegler, Chaoul, & Cohen, 2008; Carson et al., 2007). Educational groups and coping skills training have been found to be beneficial for reduction of fatigue and depressed mood, while increasing vigor (Ganz & Bower, 2007; Helgeson et al., 2001). In addition, supportive group and individual psychotherapy have been reported to have positive effects on fatigue (Ganz & Bower, 2007; Given et al, 2002) indicating that several psychosocial interventions could be used to ameliorate fatigue in cancer survivors. The National Comprehensive Cancer Network (NCCN) Fatigue Practice Guidelines recommend interventions

depending on severity of symptoms (NCCN, 2009). Education and usual care were recommended for mild fatigue. For moderate or severe fatigue, a comprehensive assessment, education and counseling (e.g., stress management, cognitive reframing, support groups), and cause specific interventions (e.g., anemia and hypothyroid therapy) were recommended. Other non-pharmacological interventions included promoting physical activity, nutrition, restorative therapy (e.g., meditation, increasing psychosocial interactions), and sleep therapy. Pharmacological interventions include psychostimulants, antidepressants, and steroids (Mock, 2001; NCCN, 2009). Emerging research is indicating that modafinil may have positive effects on fatigue, although more studies are needed (Breitbart & Alici, 2008). Hence, a wide variety of interventions can be employed to reduce fatigue, which may impact perceived cognitive and work limitations.

Interventions for Cognitive Limitations. Immerging evidence is indicating that a Cognitive Behavioral Therapy (CBT) protocol tailored to address cognitive problems improved self-reported cognitive limitations, neuropsychological cognitive decline in memory and attention, and quality of life in early-stage BCS on average eight years post-treatment (Ferguson et al., 2007). This intervention is named the Memory and Attention Adaptation Training (MAAT) and included four main components: educational components on memory and attention, self-awareness training, self-regulation techniques (e.g., relaxation training, activity scheduling, and pacing), and learning cognitive compensatory strategies (e.g., verbal rehearsal, external cues). The effects of this intervention were evident at

six months follow-up (Ferguson et al., 2007). More research and replication studies are needed to examine the efficacy/effectiveness of this MAAT on BCS.

Interventions for Depressive Symptoms. Regarding depressive symptoms, research indicates that antidepressants, several psychotherapies, and combination therapy (antidepressants and psychotherapy) are effective and efficacious (de Maat et al., 2007; Markowitz, 2008; Nathan & Gormon, 2002; Savard et al., 2006). For moderate, chronic depression, a meta-analysis found that combination therapy was most efficacious. However, for mild and moderate non-chronic depression, the efficacy and effectiveness of the different treatment modalities were comparable (de Maat et al., 2007; Nathan & Gorman, 2002). The effects of antidepressants usually have a quicker onset (e.g., usually two to six weeks) than that of psychotherapy; however, medications for depression have not shown long-term benefits after discontinuing the medication regiment (Markowitz, 2008). Evidence based psychotherapies for depression include Cognitive Behavioral Therapy (CBT), interpersonal psychotherapy (IPT), cognitive therapy, and behavioral therapy (Markowitz, 2008; Savard et al., 2006). Evidence based psychotherapies have been associated with short-term and long-term benefits (e.g., symptom relief during therapy, and learning skills and triggers serves as prophylaxis against relapse and recurrence) and fewer side effects than pharmacological treatments (Markowitz, 2008). Furthermore, psychotherapies, such as CBT and cognitive therapy, have been found to also reduce anxiety levels, fatigue, and insomnia symptoms in BCS up to six months after termination of psychotherapy (Markowitz, 2008; Savard et al., 2006).

Subclinical Depression & Work Limitations. The current study indicated that even subclinical depressive symptoms are related to work and cognitive limitations. It may be extrapolated that evidence based psychological interventions or antidepressants may be helpful in improving cognitive and work performance in both BCS and women who have never had cancer. The clinical implications from the results of this study indicate that these interventions may help ameliorate symptom burden for BCS and women without a history of cancer, which may then improve work functionality and perceived cognitive limitations. Future research should explore these implications in randomized control trials.

Public Health & Occupational Health Implications

The BCS community is large and continues to grow as medical technology, and early screening improves for breast cancer. Furthermore, a large percentage of BCS who worked prior to diagnosis, continue to work shortly after diagnosis and treatment. Hence, focusing interventions and outreach with this population to improve work productivity can have potential economic benefits to employers (Yarbroff et al., 2004), as well as economic and psychological benefit to the survivor (Bradley & Bednarek, 2002; Maunsell et al., 2004).

The results of this study, combined with data from other studies indicate the need for clinical evaluations and interventions for occupationally active BCS. Wefel and colleagues (2008) reported the results from a 2007 online survey from the Hurricane Voices Breast Cancer Foundation. While 62 percent of BCS reported a decline in their social, occupational and cognitive functioning, only five percent sought clinical evaluation (e.g., neuropsychological testing). The results

of this current study mirror the trends found in the review by Wefel and colleagues (2008).

In the current study, BCS reported significantly more perceived cognitive limitations and work limitations than NCCG; however, only 2.7 percent of BCS reported receiving a clinical neuropsychological evaluation for their cognitive function. This highlights the underutilization of clinical assessment of cognitive and occupational function in this population. Several factors could influence the lack of BCS seeking neuropsychological evaluations for difficulties (e.g., the cognitive deficits are subtle, neuropsychological tests are time consuming and require time away from work, neuropsychological evaluations are expensive, and stigma associated with seeking a psychological or neuropsychological evaluation). Hence, it is important for psychologists and neuropsychologists to establish programs that promote and conduct comprehensive clinical assessments when appropriate. However, most BCS will not seek out comprehensive clinical assessments. Hence, there is room for more efficient public health efforts to reach these individuals for evaluation, and perhaps population health interventions through workplace awareness campaigns and psychoeducation on the common difficulties experienced after cancer and possible interventions that could help ameliorate cognitive and work decline. Furthermore, work place interventions in the realm of cognitive and occupational functioning would be beneficial to occupationally active BCS. By establishing large scale educational and occupational interventions targeting factors that affect work limitations (e.g., depressive symptoms, fatigue, perceived cognitive

limitations), BCS could improve their functioning at work, which may also manifest in better overall quality of life. In addition, large population-based educational efforts could also be aimed at informing employers of difficulties their employees might experience post-cancer, factors impacting these difficulties and decline in functioning, and appropriate and cost-effective steps employers could take to increase their BCS employees return to work and decrease work limitations, such as encouraging frequent breaks and pacing of tasks (commonly used in fatigue interventions), providing a supportive environment, and adding flexibility to schedules for medical appointments (Bouknight, Bradley & Luo, 2006).

Research Implications

Measures of Cognitive Function. The results of this study indicate that BCS experience cognitive decline that may not be captured in neuropsychological screening. These findings were consistent with that found from a British sample of BCS (Shilling & Jenkins, 2007). These results indicate that future studies should focus on developing a neurocognitive screen or battery that also captures perceived functioning. Until research develops such a measurement tool, measures of perceived functionality (e.g., cognitive and occupational when applicable) should be incorporated whenever neurocognitive performance tests are administered with BCS.

Investigating Contributions of Race. There is evidence in the literature that race may be a factor in the way symptom burden is expressed (Paskett et al., 2008). Paskett and colleagues (2008) investigated racial differences in symptom

burden with 5,021 BCS and 88,352 women without a history of breast cancer. When compared to Caucasian BCS, African American BCS reported worse physical functioning, general health, and greater role limitations due to emotional health. When compared to African American women without a history of breast cancer, African American BCS endorsed worse general health and vitality. The Paskett et al. (2008) study emphasized the importance of race in symptom burden expression. At this point, it is unclear if race would have a significant difference in the assessment/measurement of cognitive and work limitations. Despite a concerted effort to recruit in diverse areas and populations, the current study was unable to obtain a racially diverse sample. Future studies should aim at investigating the impact of race on self-reported symptom burden and measures of functionality (e.g., cognitive function, work function).

Other Chronic Illnesses. Our study only compared BCS to NCCG. While, this is acceptable and relevant to the research question, future studies should use an additional disease-specific reference group, such as another cancer group or chronic illness group (Vardy et al., 2008; Vardy, Rourke, & Tannock, 2007) to determine if these trends and subsequent clinical implications were specific to BCS or relevant to other chronic illness populations.

Summary of Conclusion.

In sum, self-report measures of cognitive limitations were significantly associated with work limitations in contrast to performance-based measures. This elucidates the importance of measuring both perceived and performance based functioning in a clinical assessment encounter when a BCS seeks

assistance. Furthermore, research should aim at developing a clinical measure that portrays both perceived and performance based cognitive limitations.

Despite reporting more work and cognitive limitations, BCS were unlikely to seek assistance or assessment for these decrements in functioning. Hence, this study highlights the need for a variety of clinical specialties (e.g., psychologists, occupational therapists, public health experts) to implement work place interventions focused on psychoeducation of cognitive and work limitations, depressive symptoms and fatigue in BCS. Generalized interventions to address factors related to work limitations could benefit the work productivity and perceived cognitive limitations in BCS. More research and innovative clinical and public health approaches should be implemented in the work place to address these findings.

Table 1
CNSVS Test Summary

Cognitive Domain	Subtest	Description
Memory	Verbal Memory Test (VBM)	Participants are asked to remember 15 words and recognize them in the presence of 15 distractor words. The task is done at the beginning (short delay) and towards the end (long delay) of the battery. The lower the score, the more verbal memory impairment is present.
	Visual Memory Test (VIM)	Participants are asked to remember 15 geometric shapes and recognize them in the presence of 15 distractor shapes. The task is given at the beginning (short delay) and towards the end (long delay) of the battery. The lower the score, the more visual impairment is present.
Attention	Continuous Performance Test (CPT)	This test measures sustained attention. Participants are required to attend to the stimulus "B". The target stimulus is randomly presented 40 times, and non-target stimuli are presented 160 times. Participants must respond to the designated stimuli when flashed on the screen. A long response time may suggest cognitive impairment. Errors (more than four) are indicative of attention problems.
Executive Function	Shifting Attention Test (SAT)	The SAT measures executive control and cognitive flexibility. Individuals are tested on accuracy and speed when asked to shift instructions. In one task, participants are shown a main shape and two shapes at the bottom of the screen. They are asked to match shapes either by shape or color. The task shifts at random. Participants are to make as many correct matches as possible.

Source: CNSVS Assessment Scoring Report; retrieved from http: www.cnsvs.com

Table 2. Participant Characteristics

	BCS (n=75)		NCCG (n=75)	
	n	**%**	**N**	**%**
		Age**		
≤ 40 years old	26	34.7	45	60.0
41-50 years old	28	37.3	11	14.7
51-65 years old	21	28.0	19	25.3
Mean (Standard Deviation)	43.79 (9.04)		40.03 (11.50)	
		Race*		
Caucasian	69	92	54	72
African American	2	2.7	11	14.7
Asian American/Pacific Islander	3	4.0	5	6.7
Other	1	1.3	5	6.7
		Ethnicity		
Hispanic	3	4.2	8	11.3
Non-Hispanic	68	95.8	63	88.7
		Education		
Some College or less	13	17.3	10	13.3
Associates/Bachelors	25	33.3	27	36.0
Some Graduate School	8	10.7	11	14.7
Graduate Degree	29	38.7	27	36.0
		Marital status*		
Single	7	9.3	17	23.0
Cohabitating	3	4.0	7	9.5
Married	56	74.7	39	52.7
Divorced	9	12.0	11	14.9
Widowed	0	0	0	0

*$p<0.05$

**$p=0.000$

Note: Participant demographics (N=150). Chi-square analysis indicated that the two groups differed in age (p=0.000), race (p=0.01) and marital status (p=0.03). There were no significant differences in ethnicity (p=0.12) and education (p=0.80). Both groups indicated that they were highly educated (e.g., 87 percent of BCS and 90 percent of NCCG indicated having an associates degree or higher).

Table 3. Job characteristics of all participants

	BCS (n=75)		NCCG (n=75)	
	n	**%**	**n**	**%**
Current Job Characteristics				
Managerial	27	36.5	30	40.0
Non-Managerial	40	54.1	41	54.7
Self-Employed	7	9.5	4	5.3
Primary Occupation				
Clerical	5	6.8	4	5.3
Sales	6	8.2	2	2.7
Management/Administration	27	37.0	32	42.7
Professional/ Technical/Science	34	46.6	34	45.3
Service Worker	1	1.4	3	4.0
Years at Current Job				
1 year or less	7	10.3	13	20.3
2-5 years	27	39.7	24	37.5
6-10 years	17	25.0	13	20.3
11-15 years	9	13.2	6	9.4
16-20 years	5	7.4	3	4.7
21-25 years	1	1.5	5	7.8
26+ years	2	2.9	0	0.0
Mean (Standard Deviation)	7.18	(6.27)	6.55	(6.61)
Job Satisfaction*				
Enjoy Job/Work Hard	60	80.0	46	61.3
Enjoy Job/Don't Work Hard	9	12.0	10	13.3
Don't Like Job/Work Hard	3	4.0	15	20.0
Don't Like Job/Don't Work Hard	3	4.0	4	5.3
Annual Income				
10-19,000	1	1.3	1	1.4
20-39,000	3	4.0	9	12.2
40-59,000	6	8.0	9	12.2
60-79,000	10	13.3	18	24.3
80-99,000	8	10.7	8	10.8
100,000 or more	47	62.7	29	39.2

¥ For breast cancer survivors only

Note: Not all participants responded to all questions

*$p<0.05$

Note: Job characteristics for both groups (N=150). Chi-square analyses revealed no significant differences in years at job (p=0.23), annual income (p=0.70), and type of employment (p=0.48). No significant changes in job characteristics after cancer (p=0.07). BCS reported more job satisfaction than NCCG (p=0.02).

Table 4. Breast Cancer Survivors: Treatment and Work Absence (n= 75)

	n	%		n	%
Tumor Location			Time Since Primary Treatment		
Right Breast	41	54.7	1 year	27	36.0
Left Breast	33	44.0	2 years	17	22.7
Both Breasts	1	1.3	3 years	7	9.3
Tumor Stage			4 years	10	13.3
0	2	2.7	5 years	5	6.7
I	28	37.3	6 years	1	1.3
II	33	44.0	7 years	2	2.7
III	12	16.0	8 years	0	0.0
Treatment			9 years	3	4.0
Chemotherapy	61	81.3	10 years	2	2.7
Radiation Therapy	55	73.3	Mean (S.D.)	2.89	(2.34)
Surgery	74	98.7			
Tamoxifen or Ralozifene	33	44.0	Work absence after cancer diagnosis		
			No absence	27	36.0
Herceptin (Trastuzumab)	12	16.0	1 day to < 6 months	32	42.7
			6 to < 12 months	8	10.7
Other Treatment	18	24.0	12 to < 18 months	7	9.3
Menopausal Status			≥ 18 months	1	1.3
Premenopausal Pre and Post-Cancer	32	42.7			
Premenopausal Pre-Cancer/ Menopausal Post-Cancer	35	46.7			
Menopausal prior to cancer	7	9.3			

Note: Stage IV survivors were excluded from the study.

Table 5. Factors related to work limitations: BCS and NCCG in separate regressions (Continuous WLQ Output Score)

	BCS (n= 68)	NCCG (n=66)
	Beta (β)	Beta (β)
	Step 1: Confounding Factors	
Fatigue (MFSI)	0.23*	N/A
Depression (HADS-D)	0.11	0.24*
Pain (VAS-P)	N/A	0.11
Stage III Cancer	0.19	N/A
	R^2=0.43**	R^2= 0.25**
	Step 2: Performance Testing	
Composite Memory	1.77	0.20
Verbal Memory	-0.90	-0.27
Visual Memory	-1.12	0.07
Executive Function	-0.15	-0.97**
Attention	0.07	0.84*
	R^2= 0.47**	R^2= 0.35**
	R^2 Change= 0.04	R^2 Change= 0.10
	Step 3: Self-report	
CSC Memory	1.16	-0.56
CSC Attention	0.49	-0.86
CSC Executive Function	1.20	-0.51
CSC Overall	-2.42	1.51
Fact Cog PCI	-0.32	-0.20
Fact Cog PCIQOL	-0.07	-0.51**
	R^2= 0.66**	R^2= 0.63**
	R^2 Change= 0.19**	R^2 Change= 0.28**

*p<0.05

**p=0.000

Note: For BCS, proposed confounders accounted for 43% of the variance in work limitations (R^2=0.43, p=0.000), and self-report measures of cognitive function accounted for 19% of the variance in work limitations (R^2=0.19, p=0.000) after accounting for proposed confounders and performance tests. Performance tests did not significantly account for the variance in work limitations (R^2 Change=0.04, p=0.57) after accounting for proposed confounders. The overall model accounted for 66% of the variance in work limitations for the BCS group (R^2=0.66, p=0.000). Fatigue significantly accounted for variance in work limitations (β=0.23, p=0.04) in the BCS group.

For NCCG, proposed confounders accounted for 25% of the variance in work limitations (R^2=0.25, p=0.000) and self-report measures of cognitive performance accounted for 28% of the variance of work limitations (R^2=0.28, p=0.000) after accounting for proposed confounders and performance tests. Performance tests did not significantly account for the variance in work limitations (R^2=0.10, p=0.14) after accounting for proposed confounders. The overall model was significant (R^2=0.66, p=0.000). Depressive symptoms significantly accounted for work limitations in the NCCG (β=0.24, p=0.02).

Table 6. Factors related to work limitations: BCS and NCCG in separate regressions (Dichotomous WLQ score)

	BCS (n= 68) OR	NCCG (n= 66) OR
	Block 1: Confounding Factors	
Fatigue (MFSI)	1.17 (95% CI= 0.57, 2.17)	N/A
Depression (HADS-D)	1.40 (95% CI= 0.81, 2.42)	1.08 (95% CI= 0.82, 1.42)
Pain (VAS-P)	N/A	1.27 (95% CI= 0.79, 2.05)
Stage III Cancer	1.15 (95% CI= 0.00, 343.09)	N/A
	Block Chi Square$_{(3)}$ = 23.07**	Block Chi Square$_{(2)}$ = 10.12**
	Model Chi Square$_{(3)}$ = 23.07**	Model Chi Square$_{(2)}$ = 10.12**
	Block 2: Performance Testing	
Composite Memory	0.28 (95% CI= 0.02, 4.29)	1.11 (95% CI= 0.53, 2.30)
Verbal Memory	2.11 (95% CI= 0.40, 11.02)	0.90 (95% CI= 0.58, 1.40)
Visual Memory	2.47 (95% CI= 0.41, 15.00)	1.00 (95% CI= 0.62, 1.58)
Executive Function	1.36 (95% CI= 0.70, 2.65)	0.85 (95% CI= 0.70, 1.03)
Attention	0.60 (95% CI= 0.26, 1.35)	1.28 (95% CI= 0.97, 1.68)
	Block Chi Square$_{(5)}$ = 12.07*	Block Chi Square$_{(5)}$ = 7.50
	Model Chi Square$_{(8)}$ = 35.14**	Model Chi Square$_{(7)}$ = 17.63*
	Block 3: Self-report	
CSC Memory	0.05 (95% CI= 0.00, 8.11)	0.58 (95% CI= 0.09, 3.68)
CSC Attention	0.08 (95% CI= 0.00, 8.44)	0.65 (95% CI= 0.10, 4.37)
CSC Executive Function	0.04 (95% CI= 0.00, 4.81)	0.72 (95% CI= 0.10, 5.31)
CSC Overall	19.47 (95% CI= 0.14, 2632.66)	1.54 (95% CI= 0.23, 10.34)
Fact-Cog PCI	0.96 (95% CI= 0.78, 1.19)	0.97 (95% CI= 0.87, 1.08)
Fact Cog PCIQOL	0.29 (95% CI= 0.08, 1.03)	0.51* (95% CI= 0.29, 0.90)
	Block Chi Square$_{(6)}$ = 16.49*	Block Chi Square$_{(6)}$ = 10.18
	Model Chi Square$_{(14)}$ = 51.63**	Model Chi Square$_{(13)}$ = 27.81*

*p<0.05;**p=0.000

Note: For the BCS, the overall model was significant (p=0.000). All three blocks significantly contributed to the total Chi-Square (Confounder Chi-Square=23.07, df=3, p=0.000; Observed Cognitive Limitations Chi-Square=12.07, df=5, p=0.03; Perceived Cognitive Limitations Chi-Square=16.49, df=6, p=0.01). For the NCCG, the overall model was significant (p=0.000). Only proposed confounders significantly contributed to the total Chi-Square (Confounder Chi-Square=10.12, df=2, p=0.000; Cognitive Performance Test Chi-Square=7.50, df=5, p=0.19; Self-report of Cognitive Limitations Chi-Square=10.18, df=6, p=0.12).

Table 7. Factors and interactions related to work limitations (Continuous WLQ Output Score)

	N = 133 Beta (β)
Step 1: Confounding Factors	
Cancer Status	-0.03
Depression (HADS-D)	0.21*
Pain (VAS-P)	0.26**
Fatigue (MFSI)	-0.29*
	R^2= 0.34**
Step 2: Performance Testing	
Composite Memory	1.29
Verbal Memory	-0.80
Visual Memory	-0.69
Executive Function	-0.45*
Attention	0.33
	R^2= 0.38**
	R^2 Change= 0.04
Step 3: Self-Report	
CSC Memory	-0.31
CSC Attention	-0.36
CSC Executive Function	-0.06
CSC Overall	0.80
Fact Cog PCI	-0.24
Fact Cog PCIQOL	-0.34**
	R^2= 0.64**
	R^2 Change= 0.26**
Step 4: Interactions	
Cancer x Depression	-0.17
Cancer x Fatigue	0.28
	R^2= 0.65**
	R^2 Change= 0.01

*p<0.05

**p=0.000

Note: Confounders (R^2=0.34, p=0.000) significantly accounted for the variance in work limitations score. After accounting for the contributions of proposed confounders, cognitive performance testing did not significantly account for the variance in work limitations (R^2= 0.04, p=0.18). After accounting for the contributions of proposed confounders and cognitive performance tests, self-report of cognitive limitations (R^2=0.26, p=0.000) significantly accounted for the variance in work limitations score. After accounting for the contributions of proposed confounders, cognitive performance tests, and self-report of cognitive limitations, interaction variables for cancer status by depression and cancer status by fatigue were not significant (R^2=0.01, p=0.18).

Table 8. Multivariate comparison of symptom burden, self-reported and observed cognitive function: BCS and NCCG

(N=132)	Mean	Standard Deviation	F
Overall Model	--	--	4.71**
HADS Anxiety$^{\Phi}$			2.71
BCS	7.55	2.99	
NCCG	6.87	2.43	
HADS Depression$^{\Phi}$			8.30**
BCS	4.29	3.30	
NCCG	2.95	2.57	
MFSI Fatigue$^{\Phi}$			19.59**
BCS	4.99	4.50	
NCCG	2.05	2.49	
VAS Fatigue$^{\Phi}$			10.29**
BCS	6.00	2.43	
NCCG	4.80	2.04	
VAS Pain$^{\Phi}$			
BCS	2.85	1.76	3.53
NCCG	2.64	1.95	
CSC Memory$^{\Phi}$			39.82**
BCS	8.67	6.13	
NCCG	3.15	2.83	
CSC Attention$^{\Phi}$			3.18
BCS	4.79	3.66	
NCCG	3.44	3.08	
CSC Exec. Funct.$^{\Phi}$			18.37**
BCS	4.11	4.66	
NCCG	1.55	1.78	
CSC Overall$^{\Phi}$			24.00**
BCS	17.13	12.83	
NCCG	7.93	6.28	
Fact Cog PCI$^{\Psi}$			40.42**
BCS	53.24	17.34	
NCCG	69.21	8.32	
Fact Cog PCIQOL$^{\Psi}$			24.95**
BCS	11.38	4.57	
NCCG	14.34	2.61	

*p<0.05

**p=0.000

Note: Covariates = marital status, race, age

Φ = Higher scores indicate poorer functioning

Ψ = Lower scores indicate poorer functioning

Table 8. Multivariate comparison of symptom burden, self-reported and observed cognitive function: BCS and NCCG

	Mean	Standard Deviation	F
CNSVS Composite Memory$^{\Psi}$			1.60
BCS	103.48	16.98	
NCCG	99.12	19.52	
CNSVS Verbal Memory$^{\Psi}$			1.62
BCS	101.01	15.44	
NCCG	97.21	19.61	
CNSVS Visual Memory$^{\Psi}$			0.69
BCS	104.49	16.42	
NCCG	101.32	16.18	
CNSVS Executive Function$^{\Psi}$			1.82
BCS	99.41	7.81	
NCCG	95.96	14.37	
CNSVS Attention$^{\Psi}$			0.83
BCS	45.95	6.13	
NCCG	45.05	10.35	

*p<0.05

**p=0.000

Note: Covariates = marital status, race, age

Φ = Higher scores indicate poorer functioning

Ψ = Lower scores indicate poorer functioning

Note: BCS group significantly reported more depressive symptoms (p=0.000), physical fatigue (p=0.000), and general fatigue (p=0.000), perceived problems with memory (p=0.000), executive functioning (p=0.000), overall cognitive functioning (p=0.000), more difficulties on the perceived cognitive impairment scale (p=0.000), and perceived cognitive impairment that affected quality of life scale (p=0.000). Anxiety (p=0.10) and self-reported attention (p=0.08) did not significantly differ between groups. Performance cognitive tests for composite memory (p=0.21), verbal memory (p=0.21), visual memory (p=0.41), executive function (p=0.18), and attention (p=0.36) did not significantly differ between the BCS and NCCG.

Table 9. Relationship between performance test scales and self-report scales with all participants (N=135)

	1	2	3	4	5	6	7	8	9	10	11	12
1. CNSVS Composite Memory	--	0.87**	0.87**	0.22*	0.23**	0.04	0.07	0.01	0.00	-0.12	-0.07	0.05
2. CNSVS Verbal Memory	0.87**	--	0.51**	0.15	0.16	0.00	0.01	-0.03	0.00	-0.09	-0.06	0.02
3. CNSVS Visual Memory	0.87**	0.51**	--	0.23**	0.23**	0.07	0.11	0.05	0.00	-0.11	-0.06	0.05
4. CNSVS Executive Function	0.22*	0.15	0.23**	--	0.99**	-0.02	0.03	-0.10	-0.02	-0.01	0.01	-0.09
5. CNSVS Attention	0.23**	0.16	0.23**	0.99**	--	-0.05	-0.01	-0.12	0.04	0.00	0.04	-0.09
6. CSC Overall	0.04	0.00	0.07	-0.02	-0.05	--	0.95**	0.82**	0.89**	-0.84**	-0.72**	0.65**
7. CSC Memory	0.07	0.01	0.11	0.03	0.01	0.95**	--	0.68**	0.78**	-0.85**	-0.69**	0.62**
8. CSC Attention	0.01	-0.03	0.05	-0.10	-0.12	0.82**	0.68**	--	0.58**	-0.65**	-0.59**	0.48**
9. CSC Executive Function	0.00	0.00	0.00	-0.02	0.04	0.89**	0.78**	0.58**	--	-0.71**	-0.64**	0.61**
10. FactCog PCI	-0.12	-0.09	-0.11	-0.01	0.00	-0.84**	-0.85**	-0.65**	-0.71**	--	0.78**	-0.69**
11. FactCog PCI QOL	-0.07	-0.06	-0.06	0.01	0.04	-0.72**	-0.69**	-0.59**	-0.64**	0.78**	--	-0.72**
12. Work Limitations Output	0.05	0.02	0.05	-0.09	-0.09	0.65**	0.62**	0.48**	0.61**	-0.69**	-0.72**	--

*p<0.05
**p=0.000
Note: Control variables were Age, Marital Status and Race
Note: Tables 9, 10, and 11 show that after accounting for demographic differences, self-report tests were highly correlated with other self-report tests and performance tests were highly correlated with other performance tests.

Table 10. Relationship between performance test scales and self-report scales with BCS (N=68)

	1	2	3	4	5	6	7	8	9	10	11	12
1. CNSVS Composite Memory	--	0.84**	0.88**	0.20	0.25*	-0.06	-0.01	-0.09	-0.08	0.00	0.02	-0.04
2. CNSVS Verbal Memory	0.84**	--	0.48**	0.13	0.18	-0.05	-0.03	-0.05	-0.05	-0.02	-0.02	0.01
3. CNSVS Visual Memory	0.88**	0.48**	--	0.19	0.24	-0.05	0.02	-0.10	-0.08	0.01	0.05	-0.07
4. CNSVS Executive Function	0.20	0.13	0.19	--	0.97**	-0.14	-0.06	-0.16	-0.16	0.15	0.19	-0.19
5. CNSVS Attention	0.25*	0.18	0.24	0.97**	--	-0.13	-0.05	-0.15	-0.16	0.15	0.20	-0.19
6. CSC Overall	-0.06	-0.05	-0.05	-0.14	-0.13	--	0.95**	0.87**	0.90**	-0.86**	-0.76**	0.69**
7. CSC Memory	-0.01	-0.03	0.02	-0.06	-0.05	0.95**	--	0.78**	0.77**	-0.85**	-0.72**	0.66**
8. CSC Attention	-0.09	-0.05	-0.10	-0.16	-0.15	0.87**	0.78**	--	0.64**	-0.77**	-0.68**	0.54**
9. CSC Executive Function	-0.08	-0.05	-0.08	-0.16	-0.16	0.90**	0.77**	0.64**	--	-0.71**	-0.67**	0.68**
10. FactCog PCI	0.00	-0.02	0.01	0.15	0.15	-0.86**	-0.85**	-0.77**	-0.71**	--	-0.81**	-0.71**
11. FactCog PCI QOL	0.02	-0.02	0.05	0.19	0.20	-0.76**	-0.72**	-0.68**	-0.67**	-0.81**	--	-0.70**
12. Work Limitations Output	-0.04	0.01	-0.07	-0.19	-0.19	0.69**	0.66**	0.54**	0.68**	-0.71**	-0.70**	--

*p<0.05
**p=0.000
Note: Control variables were Age, Marital Status and Race

Table 11. Relationship between performance test scales and self-report scales with NCCG (N=68)

	1	2	3	4	5	6	7	8	9	10	11	12
1. CNSVS Composite Memory	--	0.89**	0.86**	0.26*	0.25*	0.06	0.04	0.09	0.01	-0.20	-0.10	0.08
2. CNSVS Verbal Memory	0.89**	--	0.54**	0.17	0.17	-0.06	-0.09	-0.03	-0.04	0.10	-0.04	-0.03
3. CNSVS Visual Memory	0.86**	0.54**	--	0.28*	0.26*	0.18	0.19	0.20	0.06	-0.27*	-0.15	0.18
4. CNSVS Executive Function	0.26*	0.17	0.28*	--	0.99**	-0.02	0.04	-0.13	0.09	-0.05	-0.05	-0.07
5. CNSVS Attention	0.25*	0.17	0.26*	0.99**	--	-0.03	0.02	-0.14	0.09	-0.07	-0.04	-0.04
6. CSC Overall	0.06	-0.06	0.18	-0.02	-0.03	--	0.92**	0.86**	0.78**	-0.66**	-0.42**	0.40
7. CSC Memory	0.04	-0.09	0.19	0.04	0.02	0.92**	--	0.65**	0.72**	-0.64**	0.34**	0.35
8. CSC Attention	0.09	-0.03	0.20	-0.13	-0.14	0.86**	0.65**	--	0.45**	-0.51**	-0.42**	0.36**
9. CSC Executive Function	0.01	-0.04	0.06	0.09	0.09	0.78**	0.72**	0.45**	--	-0.52**	-0.27*	0.28*
10. FactCog PCI	-0.20	0.10	-0.27*	-0.05	-0.07	-0.66**	-0.64**	-0.51**	-0.52**	--	0.47**	-0.51**
11. FactCog PCI QOL	-0.10	-0.04	-0.15	-0.05	-0.04	-0.42**	-0.34**	-0.42**	-0.27*	0.47**	--	-0.67**
12. Work Limitations Output	0.08	-0.03	0.18	-0.07	-0.04	0.40**	0.35**	0.36**	0.28*	-0.51**	-0.67**	--

*p<0.05
**p=0.000
Note: Control variables were Age, Marital Status and Race

Table 12. Factors related to self-report and performance based measures of cognitive function: BCS and NCCG in separate regressions

	Beta (β)	Beta (β)
	Self-Report	
	BCS (n= 68)	NCCG (n= 66)
DV=Fact Cog PCI		
Fatigue (MFSI)	-0.41**	N/A
Depression (HADS-D)	-0.30**	-0.14
Pain (VAS-P)	N/A	-0.28*
Stage III Cancer	-0.10	N/A
	R^2=0.36**	R^2= 0.12*
	BCS (n= 71)	NCCG (n= 72)
DV=Fact Cog PCI QOL		
Fatigue (MFSI)	-0.46**	N/A
Depression (HADS-D)	-0.36**	-0.16
Pain (VAS-P)	N/A	-0.36**
Stage III Cancer	-0.09	N/A
	R^2=0.46**	R^2= 0.18**
	Performance Test	
	BCS (n= 73)	NCCG (n= 73)
DV=CNSVS Attention		
Fatigue (MFSI)	-0.08	N/A
Depression (HADS-D)	-0.01	-0.10
Pain (VAS-P)	N/A	0.18
Stage III Cancer	-0.03	N/A
	R^2=0.01	R^2= 0.03
	BCS (n= 73)	NCCG (n= 73)
DV=CNSVS Executive Function		
Fatigue (MFSI)	-0.10	N/A
Depression (HADS-D)	0.05	-0.06
Pain (VAS-P)	N/A	0.17
Stage III Cancer	-0.07	N/A
	R^2=0.02	R^2= 0.03

*p<0.05, **p=0.000

Note: For BCS, physical fatigue (β=-0.41, p=0.000) and depressive symptoms (β=-0.30, p=0.000) significantly contributed to Fact-Cog PCI. Physical fatigue (β=-0.46, p=0.000) and depressive symptoms (β=-0.36, p=0.000) significantly contributed to Fact-Cog PCI QOL (n=71). Physical fatigue (β=-0.08, p=0.54) and depressive symptoms (β=-0.07, p=0.56) did not significantly contribute to CNSVS attention (n=73). Physical fatigue (β=-0.10, p=0.71) and depressive symptoms (β=0.05, p=0.71) did not significantly contribute to CNSVS executive function. For NCCG, general pain (β=-0.28, p=0.02) significantly contributed to Fact-Cog PCI. General pain (β=-0.36, p=0.000) significantly contributed to Fact-Cog PCI QOL (n=72). General pain (β=0.18, p=0.14) and depressive symptoms (β=0.10, p=0.43) did not significantly contribute to the performance test of attention. General pain (β=0.17, p=0.17) and depressive symptoms (β=-0.06, p=0.64) did not significantly contribute to the executive function performance test (n=73).

Table 13. Work Limitations by Perceived and Observed Cognitive Limitation in BCS (n=75)

Work Limitations		Perceived Cognitive Limitations: CSC Memory	
		No	Yes
	No	15 (20%)	6 (8%)
	Yes	12 (16%)	48 (64%)
(X^2 p=0.000)**			
Work Limitations		Perceived Cognitive Limitations: CSC Executive Function	
		No	Yes
	No	18 (24%)	3 (4%)
	Yes	27 (36%)	27 (36%)
(X^2 p=0.005)**			
		Perceived Cognitive Limitations: CSC Attention	
Work		No	Yes
Limitations	No	19 (25.3%)	2 (2.7%)
	Yes	32 (42.7%)	22 (29.3%)
(X^2 p=0.009)**			
		Perceived Cognitive Limitations: Fact-Cog PCI	
Work		No	Yes
Limitations	No	16 (21.3%)	5 (6.7%)
	Yes	13 (17.3%)	41 (54.7%)
(X^2 p=0.000)**			
		Perceived Cognitive Limitations: Fact-Cog PCI QOL	
Work		No	Yes
Limitations	No	21 (28.8%)	0 (0%)
	Yes	26 (35.6%)	26 (35.6%)
(X^2 p=0.000)**			
		Observed Cognitive Limitations: CNSVS Composite Memory	
Work		No	Yes
Limitations	No	20 (26.7%)	1 (1.3%)
	Yes	48 (64.0%)	6 (8.0%)
(X^2 p=0.396)			
		Observed Cognitive Limitations: CNSVS Verbal Memory	
Work		No	Yes
Limitations	No	20 (26.7%)	1 (1.3%)
	Yes	50 (66.7%)	4 (5.3%)
(X^2 p=0.680)			
		Observed Cognitive Limitations: CNSVS Visual Memory	
Work		No	Yes
Limitations	No	16 (21.3%)	5 (6.7%)
	Yes	47 (62.7%)	12 (16%)
(X^2 p=0.250)			
		Observed Cognitive Limitations: CNSVS Executive Function	
Work		No	Yes
Limitations	No	20 (26.7%)	1 (1.3%)

	Yes	53 (70.7%)	1 (1.3%)

(X^2 p=0.482)

		Observed Cognitive Limitations: CNSVS Attention	
Work		No	Yes
Limitations	No	19 (25.3%)	2 (2.7%)
	Yes	52 (69.3%)	2 (2.7%)

(X^2 p=0.314)

Note: A significant number of BCS who reported the presence of cognitive limitations also reported the presence of work limitations (For CSC Memory; Fact-Cog PCI, Fact-Cog PCI QOL p=0.000; For CSC Executive Function p=0.005; For CSC Attention p=0.005). BCS who had observed cognitive limitations did not significantly report work limitations (For CNSVS Composite Memory p=0.396; CNSVS Verbal Memory p=0.680; CNSVS Visual Memory p=0.250; CNSVS Executive Function p=0.482; CNSVS Attention p=0.314).

Figure 1: Conceptual model of factors impacting work limitations in breast cancer survivors.

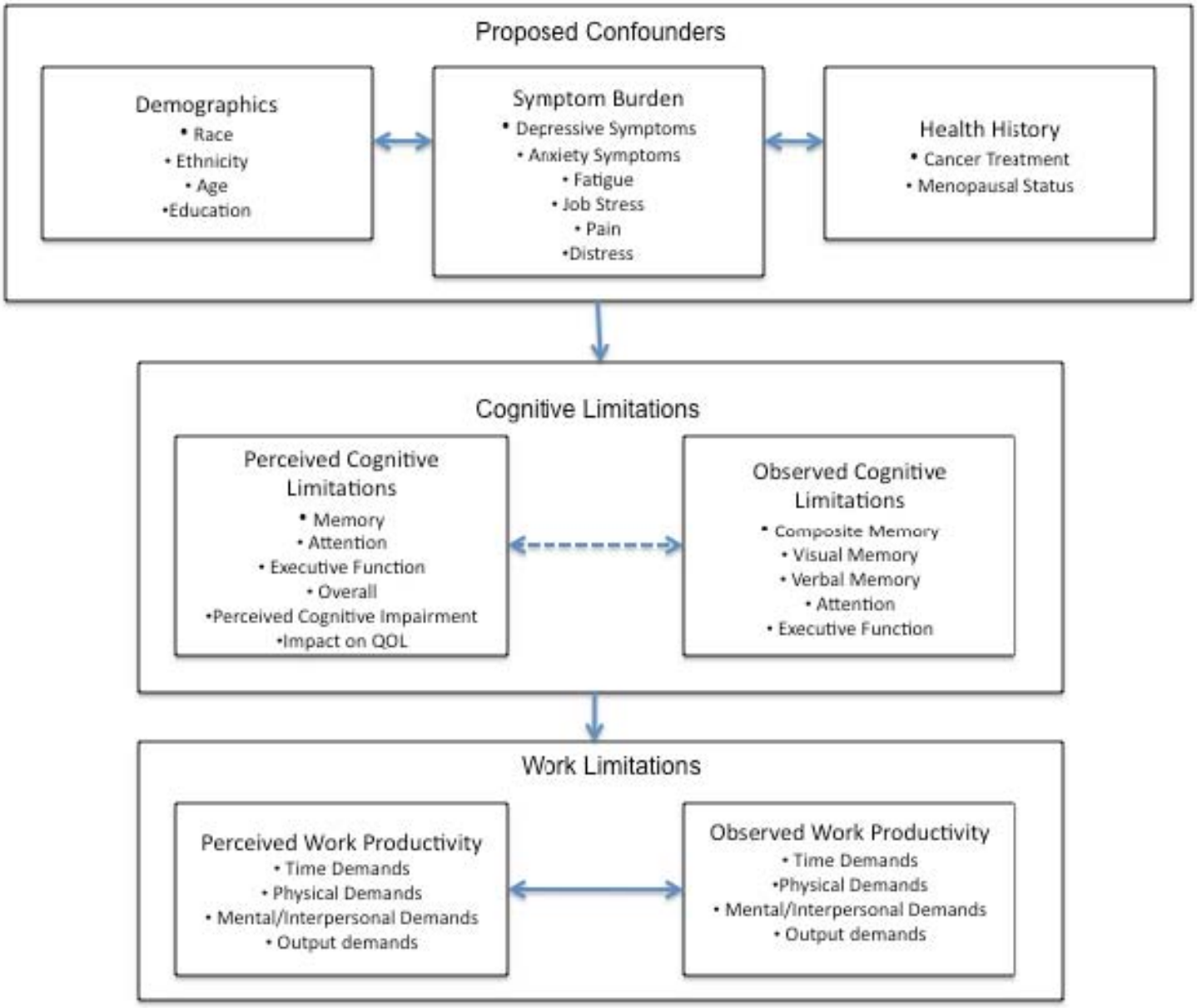


Figure 2: Flowchart of study procedures for BCS and NCCG.

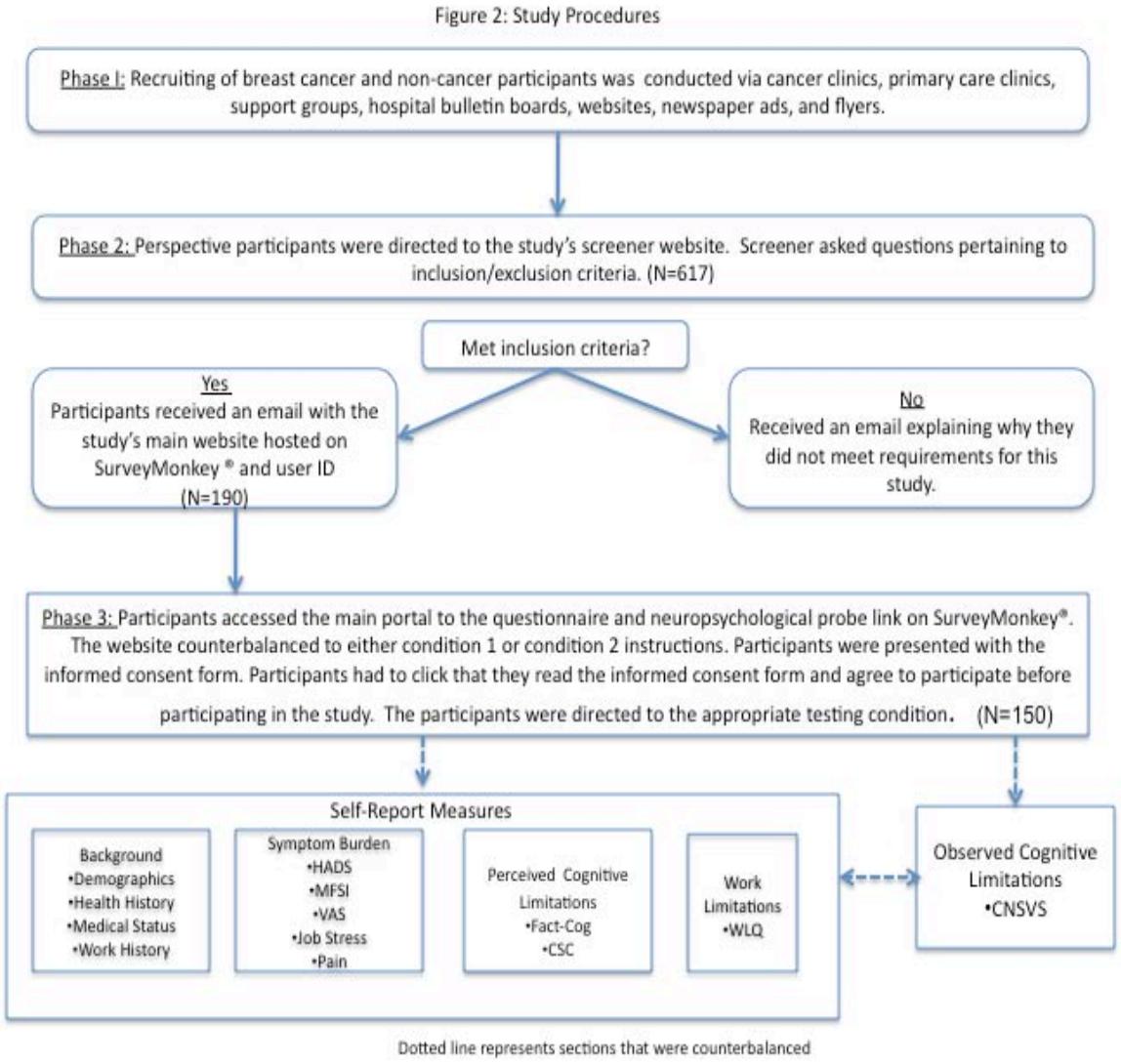


Figure 3: Self-report measures of mood, fatigue and pain (+SE) for BCS and NCCG. Items that are significant were calculated from the MANCOVA analysis (covaried for marital status, age, and race).
NOTE: For all measures in this figure, higher scores indicate poorer functioning
*p<0.05; **p=0.000

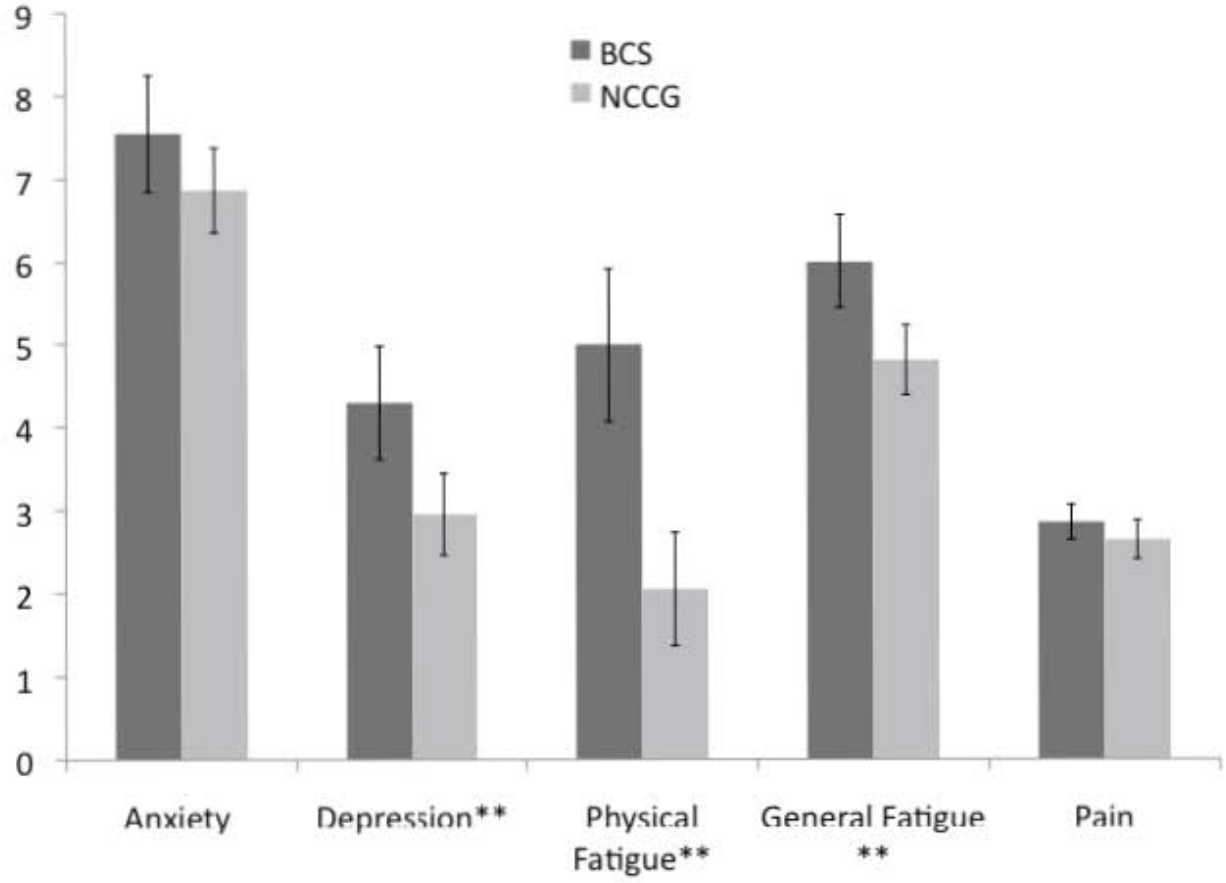


Figure 4: Self-report measures of cognitive function (+SE) for BCS and NCCG. Measures include CSC and Fact-Cog scales.
NOTE: For CSC scores, higher scores indicate poorer functioning; For Fact-Cog (FC) scores, lower scores indicate poorer functioning.
*p<0.05; **p=0.000

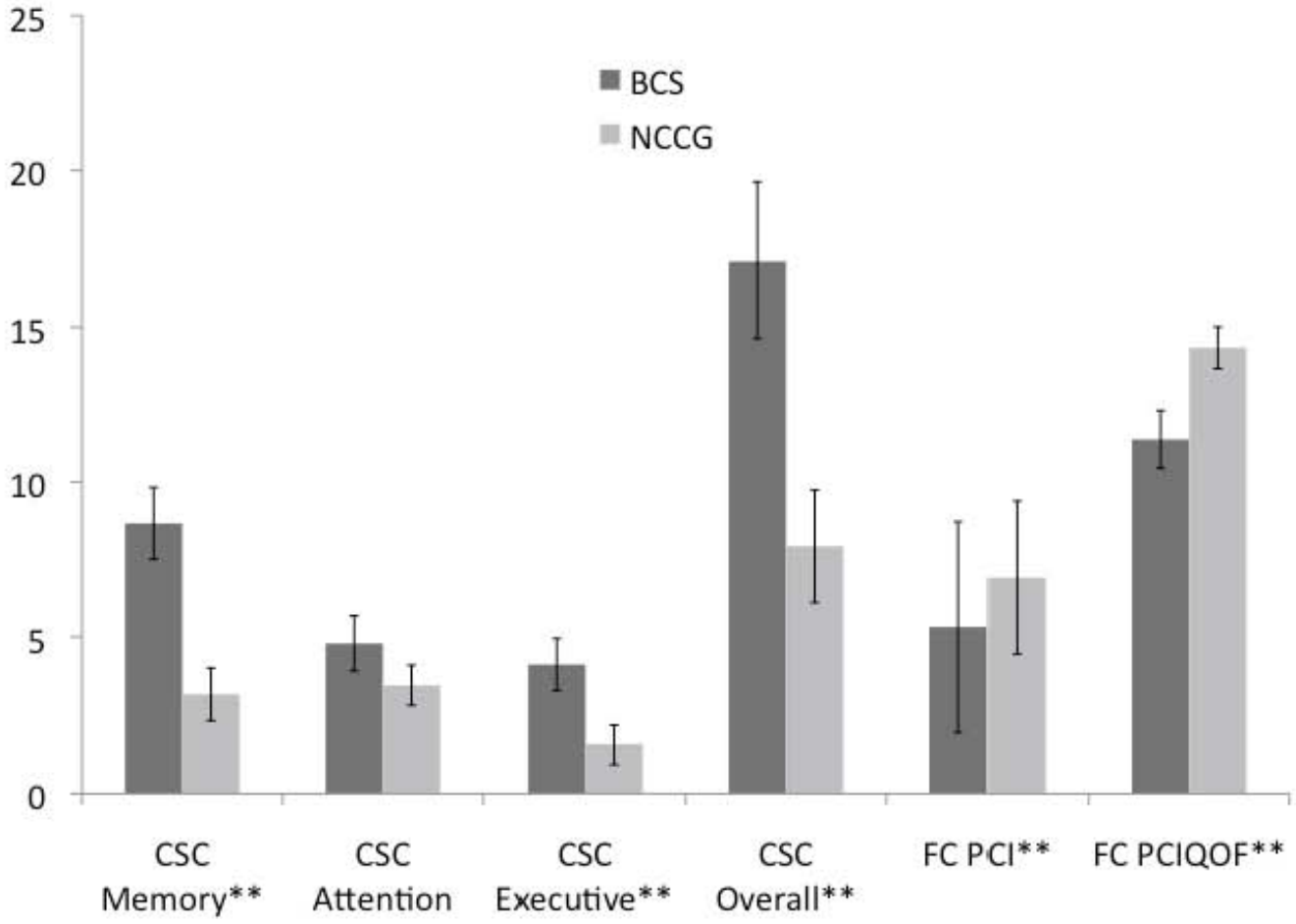


Figure 5: Cognitive performance tests (+SE) for BCS and NCCG.
NOTE: For CNSVS scores, lower scores indicate poorer functioning
*p<0.05; **p=0.000

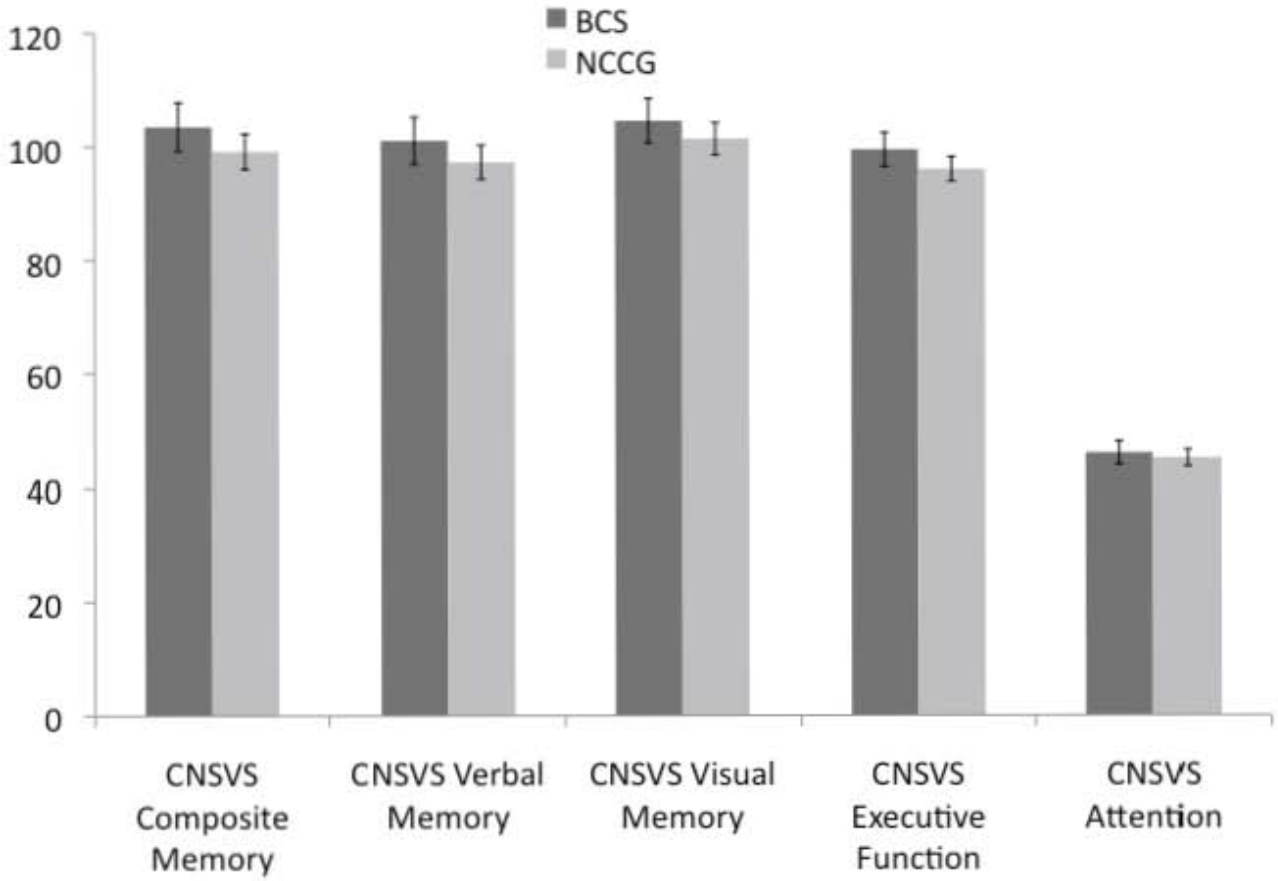
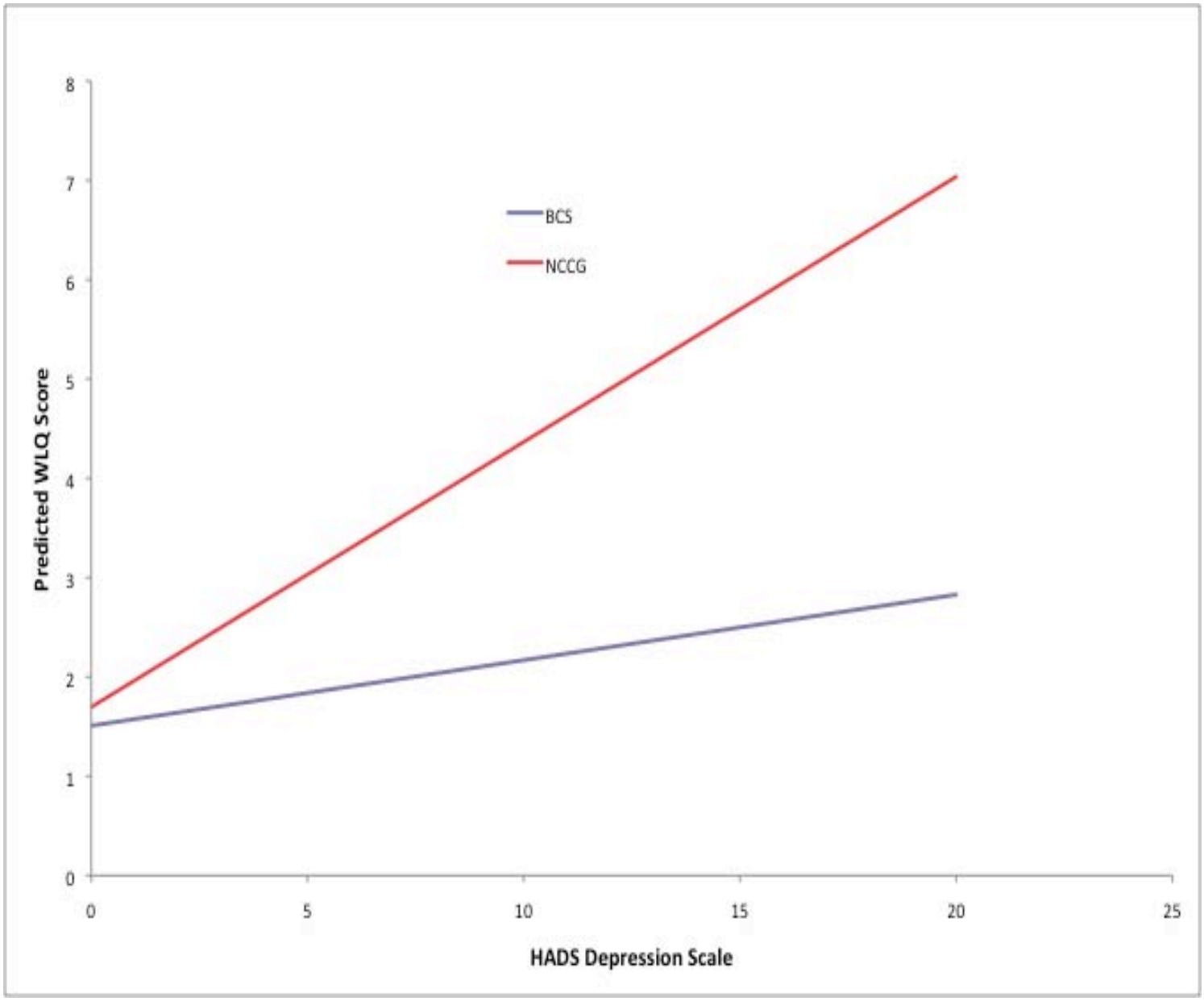
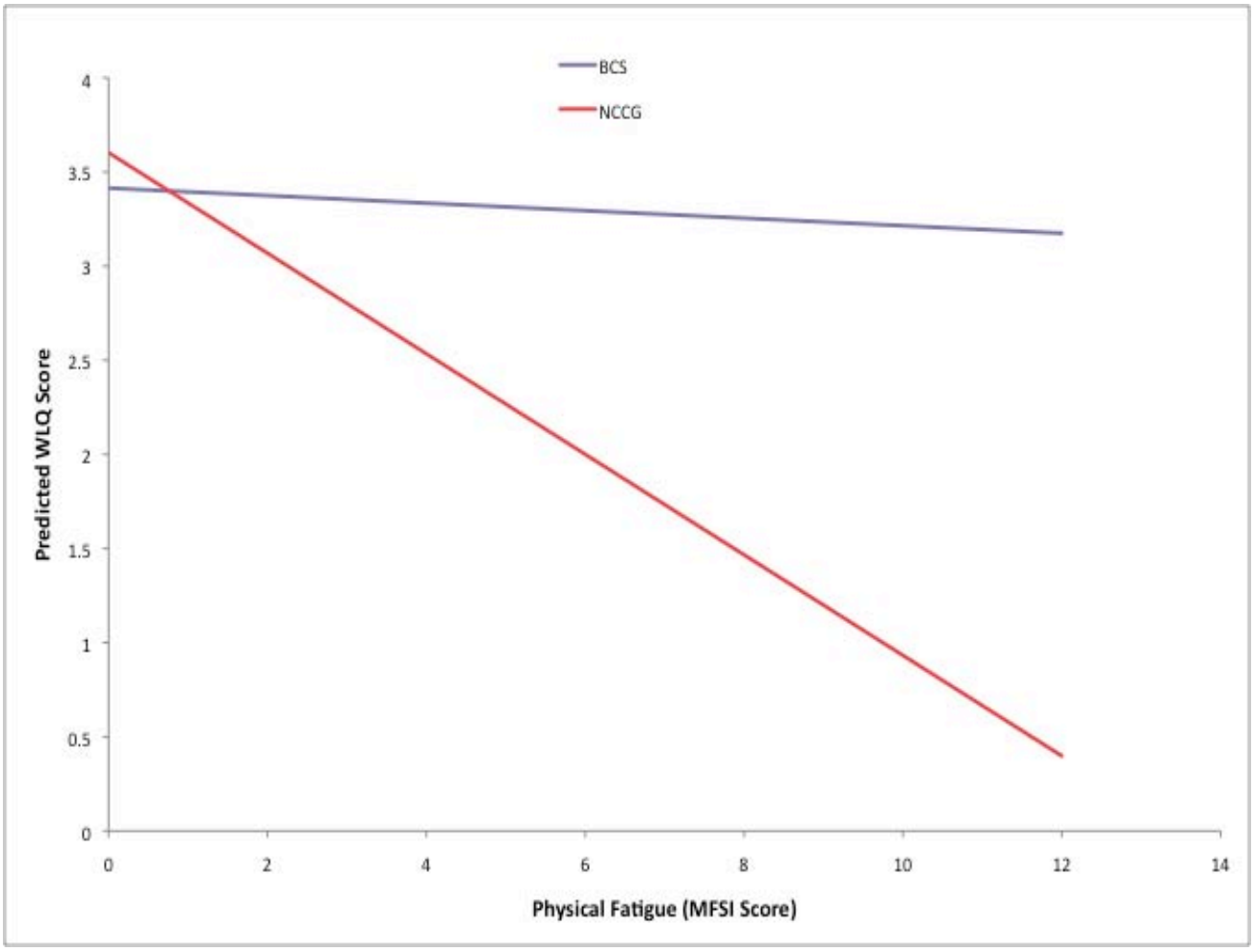


Figure 6: Predicted Work Limitations Questionnaire Score by HADS-Depression Score for BCS and NCCG (not significant).



Note: This diagram represents the interaction of HADS Depression scores by predicted WLQ score. The interactions are in the predicted direction; however, the interactions are not crossing and not statistically significant.

Figure 7: Predicted Work Limitations Questionnaire Score by MFSI-SF Physical Fatigue Score for BCS and NCCG (not significant).



Note: This diagram represents the interaction of MFSI Physical Fatigue scores by predicted WLQ score. The interactions are in the predicted direction; however, the interactions are on the edge of the data and slightly crossing and not statistically significant.

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List of Appendixes

Appendix A: Advertisements

Advertisement for Newspaper and Craig's list
Advertisement for Flyer

Are You a Working Breast Cancer Survivor OR Would You Like To Help Breast Cancer Survivors?

Women breast cancer survivors, 1 to 10 years after primary cancer treatment, whose breast cancer has not spread AND women without cancer history are needed for on-line study on cognitive function and work. Must be currently working full-time, ages 18 through 65, and without a history of adult ADHD (prior to cancer), dementia, brain injury, epilepsy, drug or alcohol abuse. You will need Internet access with connection speed faster than dial-up. Study includes completing questionnaires and a short online test of memory. The study will take approximately 60 to 75 minutes to complete. To see if you are eligible for our study, go to:

http://cim.usuhs.mil/cancerstudy

For more information call Lisseth Calvio at (301) 295-9660 or email cogworkstudy@gmail.com.

Are You A Working Breast Cancer Survivor?

Women breast cancer survivors, **1 to 10 years** after primary cancer treatment, whose breast cancer has not spread are needed for on-line study on cognitive function and work. Must be currently working full-time, ages 18 through 65, and without a history of adult ADHD (prior to cancer), dementia, brain injury, epilepsy, drug or alcohol abuse. You will need Internet access with connection speed faster than dial-up. Study includes completing questionnaires and a short online test of memory. The study will take approximately 60 to 75 minutes to complete. To see if you are eligible for our study, go to:

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For more information call Lisseth Calvio at (301) 295-9660 or email cogworkstudy@gmail.com.

Do You Want To Help Breast Cancer Survivors?

Women without cancer history are needed for on-line study on cognitive function and work. Must be currently working full-time, ages 18 through 65, and without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD. You will need Internet access with connection speed faster than dial-up. Study includes completing questionnaires and a short online test of memory. The study will take approximately 60 to 75 minutes to complete. To see if you are eligible for our study, go to:

http://cim.usuhs.mil/cancerstudy

For more information call Lisseth Calvio at (301) 295-9660 or email cogworkstudy@gmail.com.

Are You a Working Breast Cancer Survivor?

An investigation into working and cognitive function after primary treatment for cancer

In order to participate, you must be:

1) Female breast cancer survivors between 1 and 10 years since primary treatment (surgery, chemotherapy, and/or radiation) whose breast cancer has not spread

2) Currently working full-time

3) Between the ages of 18 and 65

3) Without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD (prior to cancer diagnosis)

4) Have access to the Internet (any connection speed other than dial-up)

We will ask you to take a short online questionnaire and test of memory, attention and organization that will require 60 to 75 minutes of your time**.** The study is 100% online and can be taken from any computer that does not use dial-up connection.

To see if you are eligible for our study, please go to:

http://cim.usuhs.mil/cancerstudy

For more information, you may contact Lisseth Calvio at (301)295-9660 or via email at: cogworkstudy@gmail.com

This research project is being run by the Uniformed Services University of Health Sciences, Bethesda M.D.

Want To Help Breast Cancer Survivors?

An investigation into working and cognitive function after primary treatment for cancer

In order to participate, you must be:

1) Female who has never been diagnosed with cancer

2) Currently working full-time

3) Between the ages of 18 and 65

3) Without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD

4) Have access to the Internet (any connection speed other than dial-up)

We will ask you to take a short online questionnaire and test of memory, attention and organization that will require 60 to 75 minutes of your time**.** The study is 100% online and can be taken from any computer that does not use dial-up connection.

To see if you are eligible for our study, please go to:

http://cim.usuhs.mil/cancerstudy

For more information, you may contact Lisseth Calvio at (301)295-9660 or via email at: cogworkstudy@gmail.com

This research project is being run by the Uniformed Services University of Health Sciences, Bethesda M.D.

Are You a Working Breast Cancer Survivor OR Would You Like To Help Breast Cancer Survivors?

An investigation into working and cognitive function after primary treatment for cancer

In order to participate, you must be:

1) Female breast cancer survivors between 1 and 10 years since primary treatment (surgery, chemotherapy, and/or radiation), whose breast cancer has not spread OR Female who has never been diagnosed with cancer

2) Currently working full-time

3) Between the ages of 18 and 65

3) Without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD (for breast cancer survivors, no ADHD diagnosis prior to cancer diagnosis)

4) Have access to the Internet (any connection speed other than dial-up)

We will ask you to take a short online questionnaire and test of memory, attention and organization that will require 60 to 75 minutes of your time**.** The study is 100% online and can be taken from any computer that does not use dial-up connection.

To see if you are eligible for our study, please go to:

http://cim.usuhs.mil/cancerstudy

For more information, you may contact Lisseth Calvio at (301)295-9660 or via email at: cogworkstudy@gmail.com

This research project is being run by the Uniformed Services University of Health Sciences, Bethesda M.D.

Appendix B: Random Numbers List

Random Number List

018	**101**	**140**	**095**	**139**	**060**
077	**106**	**066**	**057**	**072**	**011**
049	**002**	**104**	**045**	**079**	**013**
005	**006**	**132**	**015**	**053**	**117**
105	**051**	**014**	**092**	**116**	**009**
149	**073**	**123**	**097**	**093**	**131**
058	**046**	**020**	**059**	**100**	**080**
107	**087**	**004**	**023**	**150**	**138**
038	**062**	**068**	**125**	**047**	**144**
136	**034**	**130**	**081**	**076**	**098**
052	**024**	**056**	**063**	**007**	**090**
035	**040**	**111**	**121**	**145**	**050**
070	**010**	**026**	**091**	**033**	**135**
096	**124**	**126**	**108**	**075**	**012**
148	**094**	**120**	**082**	**074**	**067**
029	**054**	**003**	**008**	**114**	**142**
083	**019**	**027**	**103**	**088**	**044**
032	**146**	**055**	**085**	**028**	**031**
030	**122**	**089**	**110**	**021**	**042**
048	**016**	**086**	**141**	**036**	**113**
127	**147**	**064**	**133**	**001**	**118**
128	**017**	**084**	**025**	**065**	**041**
137	**102**	**134**	**078**	**069**	**109**
112	**039**	**037**	**043**	**119**	**022**
099	**071**	**129**	**115**	**061**	**143**

Appendix C: Informed Consent Form

Consent for Participation in a Research Study

The following information is provided to inform you about the research project and your participation in it. Please read this form carefully and feel free to ask any questions you may have about this study and/or about the information given below.

It is important that you understand that your participation in this study is totally voluntary. You may refuse to participate or choose to withdraw from this study at any time. If, during the course of the study, you should have any questions about the study or your participation in it, you may contact:

Lisseth C. Calvio, M.S. at 301-295-9660
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799
cogworkstudy@gmail.com

Michael Feuerstein, Ph.D., MPH at 301-295-9677
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799
mfeuerstein@usuhs.mil

Institutional Review Board Office at (301) 295-9534
USUHS, Bethesda, Maryland 20814
cogworkstudy@gmail.com

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1. INDICATED BELOW ARE THE FOLLOWING:

    a. THE PURPOSE OF THIS STUDY
    b. THE PROCEDURES TO BE FOLLOWED
    c. THE APPROXIMATE DURATION OF THE STUDY

1a. THE PURPOSE OF THIS STUDY:

- Over 80% of breast cancer survivors return to work within months of diagnosis and treatment.
- Some survivors experience memory or concentration problems that may impact their ability to work.

- This study will look at how tests and questionnaires of memory, attention, and organization might relate to each other and to your performance at work.
- If you agree to participate in this study, you will be asked to take an online questionnaire and a short test of your memory, organization and attention. The study will take approximately one hour to one hour and fifteen minutes to complete.

1b. THE PROCEDURES TO BE FOLLOWED:

Individuals meeting qualifications below may be asked to participate in the study.

You may qualify for this study based on the following:

- Adult female ages 18 to 65 years old
- Currently working full-time
- Computer/Internet access and usage; computer speed faster than dial-up (Only people with an Internet speed connection faster than dial-up will be able to continue with the study.)
- Breast Cancer Survivors Only: Between 1 and 10 years since completion of primary treatment (surgery, chemotherapy, radiation); working 1 year prior to diagnosis of cancer, and currently working.

You are not qualified of you have any of the following:

- Metastasized Cancer
- Dementia or Brain Disorder (For Example: Traumatic Brain Injury or Epilepsy)
- Drug and/or Alcohol Abuse
- Existence of adult Attention Deficit Hyperactivity Disorder (ADHD) prior to Cancer treatment

Participation in this study includes completing

1. online questionnaire (approximately 30 minutes to complete)

   and

2. a short online test of memory, organization and attention (approximately 30 minutes to complete)

1c. DURATION OF THE STUDY

Approximately 1 hour to approximately 1.25 hours

2. THIS STUDY IS BEING DONE SOLELY FOR THE PURPOSES OF RESEARCH

There will be no direct benefit to you by participating in this study. It is the goal of this research to help other cancer survivors in the future related to their ability to work.

3. DISCOMFORTS AND/OR RISKS THAT CAN BE REASONABLY EXPECTED ARE:

- The risks associated with this study are minor
    - You may find the questionnaires ask questions that may make you uncomfortable
    - You may skip questions at any time
    - Also, you may decline to participate at any time and/or withdraw your participation at any time

- You may experience discomfort or fatigue while completing the test segment
    - There will be a ample opportunities to take a break built into the study, in between sections and after each test

- If you have any questions or concerns, you can reach the principle investigators:
    - By telephone (301)295-9660
    - By email: cogworkstudy@gmail.com
    - A researcher will get back to you within one business day

4. POSSIBLE BENEFITS TO YOU THAT MAY BE REASONABLY EXPECTED ARE:

- You may gain a better understanding of the relationship between your memory, organization and attention (perceived and actual) and your productivity at work.
- Through completing this study, you will be providing information that will be helpful in expanding scientific knowledge about work productivity and memory, organization and attention function in breast cancer survivors.
- Our long-term goal is to gain a better understanding of the measurement of memory, organization and attention limitations and its impact on work productivity, and ultimately, work towards improving work productivity in cancer survivors.

5. PRIVACY AND CONFIDENTIALITY:

- All information you provide as part of this study will be confidential and will be protected to the fullest extent provided by law.
- Information that you provide and other records related to this study will be accessible to those persons directly involved in conducting this study and members of the Uniformed Services University of the Health Sciences Institutional Review Board (IRB), which provides oversight for protection of human research volunteers.
- All questionnaires, results and forms will not have identifying information and will be kept in a restricted access, password protected computer, in a locked office. Data from questionnaires will be entered into a database in which individual responses are not identified.
- Paper copies of the data will not be kept.
- Personal information will be collected for payment purposes. This information will be kept separate from the database, in a password protected computer in a locked office at the Uniformed Services University of the Health Sciences.
- If you are a military member, please be advised that under Federal Law, a military member's confidentiality cannot be strictly guaranteed.

Note: YOU ARE FREE TO WITHDRAW THIS CONSENT AND TO STOP PARTICIPATING IN THIS STUDY OR ANY ACTIVITY AT ANY TIME FOR ANY REASON.

6. COMPENSATION

- You will be given the option of receiving a book on stress reduction for completing both phases of this study
- At the end of the study, you will be asked for some personal information (e.g., name, address, social security number, phone number)in order to receive the book.
- This information is collected for tax tracking information by our institution. We must receive this information in order to render compensation.
- This information will be stored separately from the study data and will be stored in a secure, password protected computer in a locked office with restricted access.

7. RECOURSE IN THE EVENT OF INJURY:

COMPENSATION TO YOU IF YOU ARE INJURED AND LIMITS TO YOUR MEDICAL CARE: This study should not entail any physical or mental risk beyond those described above. It is believed that complications arising from participation should not occur. If, for any reason, you feel that continuing this study would constitute a hardship for you, you may end your participation in the study at any time.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, contact the Director of Human Subjects Protection Program at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799 at (301)295-9534. This office can review the matter with you. They can provide information about your rights as a research volunteer. They may also be able to identify resources available to you. If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. Information about judicial avenues of compensation is available from the University's General Counsel at (301)295-3028.

Should you have any questions at anytime about the study you may contact the principal investigator, Lisseth C. Calvio, M.S., Department of Medical and Clinical Psychology, USUHS, Bethesda, Maryland 20814-4799, at 301-295-9660.

STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS RESEARCH PROJECT:

I have read this consent form and I understand the procedures to be used in this study and the possible risks, inconveniences, and/or discomforts that may be involved. All of my questions have been answered. I freely and voluntarily choose to participate. I understand that I may withdraw at any time. By clicking on the "yes" button, you are agreeing that you have read the consent form and understand the procedures to be used in this study. You also agree that you freely and voluntarily choose to participate and understand that you may withdraw at anytime. If you wish you may print out a copy of this form for your records.

o **Yes, I agree to participate in this study.**

Appendix D: Screening Questions

Screening Questions:

Thank you for your interest in participating in our study. The following is a list of questions that will determine your eligibility for this study. We will email you within a few days after your completion of this screener.

1. Are you within the ages of 18 and 65?

2. What is your gender?

3. Are you able to access the Internet when needed?

4. Are you able to use the Internet by yourself (without help/assistance)?

5. Are you currently working full-time or self-employed? (Full-time is considered to be on average 40 hours of work or more a week)

6. On average, how many hours do you work a week?

7. Have you ever been diagnosed with any of the following: Dementia, Brain Injury, Adult Attention Deficit Hyperactivity Disorder (Adult ADHD), Epilepsy, Drug or Alcohol Abuse?

1. Have you ever been diagnosed with any form of cancer?

- **If yes, please specify the type of cancer you were diagnosed with:**

9. Have you ever been diagnosed with breast cancer?

*****The following questions are specific cancer questions- Only for those who answered yes to having a history of cancer****

1. Were you diagnosed with stage IV (metastasized) cancer?

2. Did you complete primary cancer treatment (defined as surgery, radiation therapy and/or chemotherapy) between 1 and 10 years ago?

3. Where did you receive primary cancer treatment?

4. What type of treatment have you received for your cancer (for example, lumpectomy, 3 rounds of chemotherapy)?

For all participants:

1. What is an email address where you can be contacted for the purpose of this study?

Please note that within the next few days, we will be emailing you from the following email address: cogworkstudy@gmail.com. Please ensure that your email address allows this email address to bypass any filter settings on your email. Thank you for your interest in our study.

Appendix E: Participant Instructions (Condition I and II)

Instructions (Condition I):
Thank you for your interest and participation in our study. The information that you provide will be looked at very carefully and be used in future efforts to help cancer survivors at work.

This study will be conducted in two parts and will require you to access two separate websites:

- One website will contain questionnaires
- One website will consist of some short tests of memory, attention, and organization (CNSVS).

This study will take one hour to one hour and fifteen minutes to complete. It must be completed continuously. Once you begin the first portion, you must also complete the second portion during the same time period. Also, please ensure that you complete the study in a quiet area with no or little distractions. You will be allowed to take breaks in between the short tests and in between logging into the two websites. You will be required to have a connection speed that is faster than dial-up.

Your Identification Number is:

You will be asked this number several times, including when you log on to the website with the test of memory, attention, and organization.

Please follow the order of events that is provided to you:

Click the link below:
Click Me

Or copy and paste the following website to your browser:
https://www.surveymonkey.com/s.aspx?sm=9J5uaGoq_2fhYErTylDmeycg_3d_3d

1. The first pages that you will see are the informed consent forms. Please read it carefully. You must agree to participate in the study in order to proceed.

2. You will then be presented with a series of questionnaires.

3. Upon completing the questionnaires, when you will click on the link it will open up the test in another window. **DO NOT CLOSE THE INITIAL BROWSER as you will need to return after finishing the test portion**.

4. When you log on to the test portion (CNSVS Web Agent), you will be asked for a test administrator and password. Please put “usuhs” for both.

5. The next window will ask for your “Subject ID and birthdate.

6. Your Subject ID is your participant number (provided above).

7. At the end of the study, you will be asked a few more questions for compensation purposes and given online support resources.

8. You will be done once you see the following message and click the link to end the questionnaire:

This concludes the questionnaire. You may close your browser window now. Thank you again for your participation, if you have any questions you can contact the principle investigators as listed below:

Email: cogworkstudy@gmail.com

Lisseth C. Calvio, M.S. 301-295-9660
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Michael Feuerstein, Ph.D., MPH at 301-295-9677
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Institutional Review Board Office at (301) 295-9534
USUHS, Bethesda, Maryland 20814

Thank you for your participation.

Sincerely,
Lisseth C. Calvio, M.S.
LT MSC USN
Principle Investigator
Uniformed Services University of the Health Sciences

Instructions (Condition II):

Thank you for your interest and participation in our study. The information that you provide will be looked at very carefully and be used in future efforts to help cancer survivors at work.

This study will be conducted in two parts and will require you to access two separate websites:

- One website will consist of a short test of memory, attention, and organization (CNSVS)
- One website will consist of questionnaires

This study will take one hour to one hour and fifteen minutes to complete. It must be completed continuously. Once you begin the first portion, you must also complete the second portion during the same time period. Also, please ensure that you complete the study in a quiet area with no or little distractions. You will be allowed to take breaks in between the short tests and in between logging into the two websites. You will be required to have a connection speed that is faster than dial-up.

Your Identification Number is:

You will be asked this number several times, including when you log on to the website with the test of memory, attention, and organization.

Please follow the order of events that is provided to you:

Click the link below:
Click Me

Or copy and paste the following website to your browser:
https://www.surveymonkey.com/s.aspx?sm=9J5uaGoq_2fhYErTylDmeycg_3d_3d

1. The first pages that you will see are the informed consent forms. Please read it carefully. You must agree to participate in the study in order to proceed.

2. You will take the test portion of the study first. You will be asked to click on a link that will open up the CNSVS test in another window. **DO NOT CLOSE THE INITIAL BROWSER as you will need to return after finishing the test portion**.

3. On the CNSVS site, you will be asked to log in. When you log in to the test portion (CNSVS Web Agent), you will be asked for a test administrator and password. Please put “usuhs” for both.

4. The next window will ask for your “Subject ID” and birthdate.

2. Your Subject ID is your participant number (provided above).

3. Upon completing the CNSVS test, return to the original window, and continue to fill out a few questionnaires.

4. At the end of the study, you will be asked a few more questions for compensation purposes and you will be provided a list of online support resources.

5. You will be done once you see the following message and click the link to end the questionnaire:

This concludes the questionnaire. You may close your browser window now. Thank you again for your participation, if you have any questions you can contact the principle investigators as listed below:

Email: cogworkstudy@gmail.com

Lisseth C. Calvio, M.S. 301-295-9660
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Michael Feuerstein, Ph.D., MPH at 301-295-9677
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Institutional Review Board Office at (301) 295-9534
USUHS, Bethesda, Maryland 20814

Thank you for your participation.
Sincerely,

Lisseth C. Calvio, M.S.
LT MSC USN
Principle Investigator
Uniformed Services University of the Health Sciences

Appendix F: Self-Report Questionnaires

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)*
Cognitive Symptoms Checklist-Modified (CSC; Feuerstein, Hansen, Calvio, Johnson, Ronquillo, 2007; O'Hara, Harrell, Bellingrath, & Lisicia, 1993)
Rotterdam Symptom Checklist (Jean-Pierre et al., 2006; de Haes et al., 1990)
Fatigue Visual Analogue Scale (Jean-Pierre et al., 2007)
Measure of Job Stress (from Behavioral Risk Factor Survey; CDC, 1999)
Pain Visual Analogue Scale (Scott & Huskisson, 1979)
Fact-Cog Functional Assessment of Cancer Therapy Cognitive Scale Version 2 (FACT-Cog; Wagner, Cella, & Doninger, 2003; Cella et al., 1993)
Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF; Stein, Jacobsen, Blanchard, Thors, 2004)
Work Limitations Questionnaire (WLQ; Lerner et al., 2001)

Hospital Anxiety and Depression Scale (HADS)

Please answer the following questions about how you would describe your feelings as of this moment. Please click only one response for each question.

1. I feel tense or wound up

Most of the time	A lot of the time	Occasionally	Not at all
o	o	o	o

2. I still enjoy the things I used to enjoy

Definitely as much	Not quite as much	Only a little	Hardly at all
o	o	o	o

3. I get sort of frightened feelings as if something awful is about to happen

Quite badly	Not too badly	A little	Not at all
o	o	o	o

4. I can laugh and see the funny side of things

As much as always	Not quite so much now	Definitely not so much now	Not at all
o	o	o	o

5. Worrying thoughts go through my mind

A great deal of the time	A lot of the time	From time to time	Only on occasion
o	o	o	o

6. I feel cheerful

Not at all	Not often	Sometimes	A lot
o	o	o	o

7. I can sit at ease and feel relaxed

Definitely	Usually	Not often	Not at all
o	o	o	o

8. I feel as if I am slowed down

Nearly all the time	Very often	Sometimes	Not at all
o	o	o	o

9. I get a sort of frightened feeling like butterflies in my stomach

Not at all	Occasionally	Quite often	Very often
o	o	o	o

10. I have lost interest in my appearance

Definitely	I don't take so much care as I should	I may not take quite as much care	I take just as much care as ever
o	o	o	o

11. I feel restless as if I have to be on the move

Very much	Quite a lot	Not very much	Not at all
o	o	o	o

12. I look forward with enjoyment to things

Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)
Physical Fatigue Subscale

Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes **how true each statement has been for you in the past seven days**.

	Not at all	A little	Moderately	Quite a bit	Extremely
2. My muscles ache	0	1	2	3	4
4. My legs feel weak	0	1	2	3	4
16. My arms feel weak	0	1	2	3	4
19. I ache all over	0	1	2	3	4
26. My body feels heavy all over	0	1	2	3	4

The Rotterdam Symptom Checklist

Have you during the last 3 days (week), been bothered by:

Tiredness	❑ not at all	❑ a little	❑ quite a bit	❑ very much
Lack of energy	❑ not at all	❑ a little	❑ quite a bit	❑ very much
Difficulties sleeping	❑ not at all	❑ a little	❑ quite a bit	❑ very much

Visual Analogue Scale (VAS)

Please rate the fatigue that you usually experience on a typical workday.

Measure of Job Stress (from Behavioral Risk Factor Survey- BRFS)

How often do you feel that your present work situation is putting you under too much stress?

o Never o Seldom o Sometimes o Often

Additional:

How intellectually challenging is your job? 1-10

How physically challenging is your job? 1-10

Pain Visual Analogue Scale

Please rate the severity of your pain during the *past week*.

Fact-Cog (Version 3)

Below is a list of statements that other people with your condition have said are important. **By circling one (1) number per line, please indicate how often each of the following has occurred <u>during the past 7 days.</u>**

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

Below is a list of statements that other people with your condition have said are important. **By circling one (1) number per line, please indicate how often each of the following has occurred during the past 7 days.**

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have difficulty shifting back and forth between different activities that require thinking	0	1	2	3	4

Please answer the questions below with regard to all the above concerns that you have identified. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days**.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

Below is a list of statements that other people with your condition have said are important**. By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH ^	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Below is a list of statements that other people with your condition have said are important. **By circling one (1) number per line, please indicate how often each of the following has occurred during the past 7 days.**

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
PC30	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
PC31	Other people have told me I seemed to have trouble speaking clearly	0	1	2	3	4
PC32	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
PC33	Other people have told me I seemed confused	0	1	2	3	4

		Not at all	A little bit	Some-what	Quite a bit	Very much
PC34	Other people have told me my mind seemed really sharp	0	1	2	3	4

Cognitive Symptoms Checklist – Modified (CSC)

Please read each of the following items below. They describe problems that you may or may not experience at work.

Item:	Yes	No
1. I have difficulty doing math in my head		
2. I have difficult answering questions quickly		
3. I have difficulty seeing and correcting mistakes on my own		
4. I have difficulty seeing and correcting mistakes pointed out to me by others		
5. I have difficulty focusing on a task when there is too much detail or clutter		
6. I have difficulty making decisions		
7. I have difficulty understanding what I read without rereading it		
8. I have difficulty understanding what I hear the first time I hear it		
9. I have difficulty seeing mistakes that I make as they occur		
10. I have difficulty seeing mistakes after I have completed the task		
11. I have difficulty trying new ideas or actions		
12. I have difficulty planning a speech		
13. I have difficulty shifting my attention among two or more things		
14. I have difficulty staying with a task until completion		
15. I have difficulty planning what to discuss when I meet someone		
16. I have difficulty following directions to a specific place		
17. I have difficulty shifting from 1 task or activity to another		
18. I have difficulty completing all steps of a task or activity		
19. I have difficulty following step-by-step instructions		
20. I have difficulty putting steps in order such that the most important steps are done first		
21. I have difficulty setting up a routine or system to approach tasks		
22. I have difficulty understanding what a problem is when it occurs and clearly stating what the problem is		
23. I have difficulty starting a task or activity on my own		
24. I have difficulty remembering where my car is parked		
25. I have difficulty focusing on a task when there is a sudden movement around me		
26. I have difficulty knowing where to look for information to solve a problem		
27. I have difficulty using new information to re-evaluate what I know		
28. I have difficulty choosing a solution to a problem from several possible sources		
29. I have difficulty focusing on a task when there is a lot of movement happening around me		
30. I have difficulty focusing on a task when there is a sudden loud noise		
31. I have difficulty following written instructions		
32. I have difficult writing to other people in an organized manner		
33. I have difficulty organizing information to be remembered		
34. I have difficulty focusing on a task when more than one person is speaking at a time		
35. I have difficulty focusing on a task when a radio or TV is playing in the background		
36. I have difficulty following or retracing steps to solve a problem		
37. I have difficulty remembering to perform daily routines		
38. I have difficulty remembering things someone has asked me to do		
39. I have difficulty remembering he content of telephone conversations		
40. I have difficulty focusing on a task when I feel hot or cold		
41. I have difficulty remembering the content of conversations and/or meetings		
42. I have difficulty remembering a word I wish to say		
43. I have difficulty acting on a decision that I made		
44. I have difficulty putting together the materials needed for a task		
45. I have difficulty understanding a system		
46. I have difficulty remembering my train of thought as I am speaking		
47. I have difficulty remembering the name of a familiar object or person		
48. I have difficulty understanding graphs or flowcharts		
49. I have difficulty understanding how a task fits into a plan or system		
50. I have difficulty understanding systems and models		
51. I have difficulty remembering information that is “on the tip of my tongue”		
52. I have difficulty remembering what I intended to write		
53. I have difficulty figuring out how a decision was reached		
54. I have difficulty following the flow of events		

55. I have difficulty considering all aspects of what I hear or see instead of focusing on only one part
56. I have difficulty remembering to schedule appointments
57. I have difficulty staying focused in places where there are many sights and sounds
58. I have difficulty remembering to keep appointments once they are scheduled
59. I have difficulty focusing on a task when I are in a large area

OUTCOME MEASURE

Work Limitations Questionnaire- Output Demands

These questions ask you to rate the amount of time during the **past two weeks** that you had difficulty handling certain parts of your job.

Mark the "Does not apply to my job" box only if the question describes something that is not part of your job.

In the past two weeks, how much of the time did you feel your physical or emotional problems make it difficult for you to do the following (questions 1-25)?

DIFFICULTY	All of the time (100%)	Most of the time	Half of the time (50%)	Some of the time	None of the time (0%)	Does not apply to my job
21. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to handle the workload?	o	o	o	o	o	o
22. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to work fast enough?	o	o	o	o	o	o
23. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to finish work on time?	o	o	o	o	o	o
24. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to do your work without making mistakes?	o	o	o	o	o	o
25. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to feel you've done what you are capable of doing?	o	o	o	o	o	o

Appendix G: Resources for breast cancer survivors

The following is a list of websites that give information on resources that specialize in cancer survivorship issues and/or emotional support. These websites can be utilized to seek support services if you or someone you know may be interested.

Resources

American Cancer Society
The American Cancer Society provides the public with accurate, up-to-date information on all aspects of cancer through a toll-free information line, website and published materials. Patients, family members and friends can learn about cancer and be connected to resources in their communities, 24 hours a day, seven days a week, by calling 1-800-ACS-2345 or visiting the website.
Website: http://www.cancer.org/docroot/home/index.asp

American Psychosocial Oncology Society
APOS has a toll-free Helpline through which cancer patients, caregivers and advocacy organizations may obtain referrals for local counseling services throughout the United States. This referral program aims to connect cancer patients and their caregivers to psychiatrists, psychologists, nurses, social workers and counselors skilled in the management of cancer-related distress.
To request a confidential referral, please call: Toll Free 1-866-276-7443 (1-866-APOS-4-HELP) or you may send an e-mail to the helpline at: sspencer@apos-society.org
Website: http://www.apos-society.org/

Association for Behavioral and Cognitive Therapies (ABCT)
ABCT's Find-a-Therapist service gives you access to therapists schooled in cognitive and behavioral techniques. The therapist listed in Find-a-Therapist are licensed professionals who have met the requirements of membership in ABCT and who have chosen to appear in this directory. Primarily psychologists, psychiatrists, and clinical social workers, the practitioners that participate in this service practice in a range of settings: in private practice, clinics, hospitals, and community mental health settings.
Website: http://www.aabt.org/members/Directory/Find_A_Therapist.cfm

Association of Oncology Social Work
AOSW is a non-profit, international organization of social workers dedicated to the enhancement of psychosocial services to people with cancer and their families. AOSW offers the POWER Directory to provide the opportunity for people with cancer and their families, as well as health care professionals to search this database of clinicians who may meet their needs.
Website: http://www.aosw.org/

Cancer Care, Inc
Cancer Care, Inc. is a national non-profit organization whose mission is to provide free professional help to people with all cancers through counseling, education, information and referral and direct financial assistance.
Website: http://www.cancercare.org/

Cancer Hope Network
Cancer Hope Network is a national, non-profit organization offering free, confidential, one-on-one emotional support to adult cancer patients and their caregivers. Support is provided via telephone (1-877-HOPENET) by over 325 trained volunteers who have all been through a cancer experience, have recovered and are again leading productive lives. By giving recently diagnosed patients the gift of Hope, CHN's survivors help them successfully cope with their cancer and its treatment.
Website: http://www.cancerhopenetwork.org/

Cancer Survivors' Network
The American Cancer Society's CSN is an online community created by and for cancer survivors and their families for the purpose of connecting with others like themselves, sharing practical information, and supporting one another. Listen to personal stories, post questions, chat, and connect with others going through a cancer experience.
Website: http://www.acscsn.org/

Healing Journeys
The mission at Healing Journeys is to promote and support healing by assisting people with cancer or other life-altering illnesses to access their own healing potential and their ability to thrive.
Website: http://www.healingjourneys.org/

I'm Too Young For This! Cancer Foundation For Young Adults
A TIME Magazine Best 50 Website 2007, the *I'm Too Young For This! Cancer Foundation For Young Adults* is a global support community for young adults affected by cancer who get busy living and rock on. Our mission is to end isolation and improve quality of life by providing one-stop access to hard to find resources, peer support and social networks.
Website: http://imtooyoungforthis.org/

Inflammatory Breast Cancer: IBC
The IBC Research Foundation is the only cancer research organization which specifically targets IBC and the research to find its cause. This website details symptoms and offers information and help for patients and their caregivers.
Website: http://www.ibcresearch.org/

Live Strong - Resource for Cancer Survivors
Live Strong - Resource for Cancer Survivors focuses on post-treatment and long-term survivorship topics (physical, emotional, and practical) for cancer survivors and their caregivers.
Website:
http://www.livestrong.org/site/c.khLXK1PxHmF/b.2660611/k.BCED/Home.htm

Living Beyond Breast Cancer
As a national education and support organization, their goal is to improve your quality of life and help you take an active role in your ongoing recovery or management of the disease, regardless of educational background, social support or financial means.

Website: http://www.lbbc.org/resources-links.asp

Medicare Drug Prescription Plan (Part-D) Information
Medicare's new prescription drug benefit, Medicare Part D, will start January 1, 2006 and will mean changes for many people receiving treatment for mental illness. This website has the latest information from leading mental health organizations.
Website: http://www.mentalhealthpartd.org/

MetaCancer Foundation, Inc.
The MetaCancer Foundation has launched its innovative website and offers resources for everyday living, opportunities for creative reflection, and possibilities for you to live beyond your diagnosis right now with strength, grace, and peace.
Website: http://metacancer.org/

Patient/Partner Project
The Patient/Partner Project is a multi-faceted, long-term program focused on helping cancer patients by helping their partners.
Website: http://www.thepatientpartnerproject.org/

People Living with Cancer
People Living with Cancer (PLWC) is the American Society of Clinical Oncology's (ASCO) patient information website.
Website: http://www.plwc.org/portal/site/PLWC

Pregnant with Cancer Network
The Pregnant with Cancer Network is an organization for women diagnosed with cancer during pregnancy. Their mission is to connect women who are pregnant with cancer with other women who have been pregnant with the same type of cancer. These women lend support, offer hope and share their experiences with one another through phone and e-mail conversation.
Website: http://www.pregnantwithcancer.org/

Steps for Living
Steps For Living is a non-profit clearinghouse of cancer information and human resources that uses the power of the arts to raise awareness about what it means to be a cancer survivor by educating and empowering those in need with everyday steps for living through and beyond their darkest hours.
Website: http://www.stepsforliving.org/

Strength for Caring
Strength for Caring is a program that addresses the complex needs of a person caring for a loved one with cancer. This community-based program is free of charge and provides comprehensive education and support for caregivers.
Website: http://www.strengthforcaring.com/

SuperSibs!
SuperSibs! is a national not-for-profit organization that works to honor, support and recognize the brothers and sisters of children with cancer. Their goal is to help these

"shadow survivors" re-define the cancer sibling experience and move forward in their lives with strength, courage and hope.
Website: http://www.supersibs.org/

Wellness Community
The Wellness Community is a national non-profit organization that provides in-person and online support groups and education programs to people with all cancers and their caregivers.
Website: http://www.thewellnesscommunity.org/

WomenStories
The mission of WomenStories is to produce videos about breast cancer and distribute them nationally and internationally, so information and support about this disease will be readily available to all newly diagnosed women.
Website: http://www.womenstories.org/

Appendix H: CNSVS Psychometrics Tables

Test-Retest Value Comparison of CNSVS v. Other Modalities of Neuropsychological Tests (Gualtieri & Johnson, 2006)

	Conventional	Computerized Nueropsychological Tests (General)	Headminder	CNSVS
Attention	0.70-0.73	0.6-0.63	0.58	0.65
Memory	0.67-0.71	0.65-0.69		0.66
Working Memory			0.75	
Immediate Visual Memory			0.63	
Delayed visual memory			0.81	
Verbal recognition memory			0.63	
educational index			0.91	
Psychomotor Speed	0.78-0.65	0.72-0.79		0.88
Finger Tapping	0.75-0.83	0.74-0.79		0.78
Coding	0.87-0.88	0.78-0.85		0.82
Stroop Test	0.64	0.74		0.75
Cognitive Flexibility	0.68-0.74	0.68-0.74		0.71
Reaction Time	0.82	0.66-0.68		0.75

CNSVS Correlations with Traditional Neuropsychological Tests (Gualtieri & Johnson, 2006)	
Cognitive Test/Domain	CNSVS (Correlations)
Memory	0.726
Cognitive Flexibility	0.744
Complex Attention	0.645
Verbal Memory, total correct	0.611
Visual Memory, total correct	0.668
Immediate memory, total correct	0.667
Delayed memory, total correct	0.625
Symbol digit coding, correct	0.840
Symbol digit coding, errors	0.623
Stroop test, errors	0.314
Shifting attention, correct	0.773
Shifting attention, errors	0.697
Shifting attention, efficiency	0.694
Continuous performance, correct	0.452
Continuous performance, errors	0.565